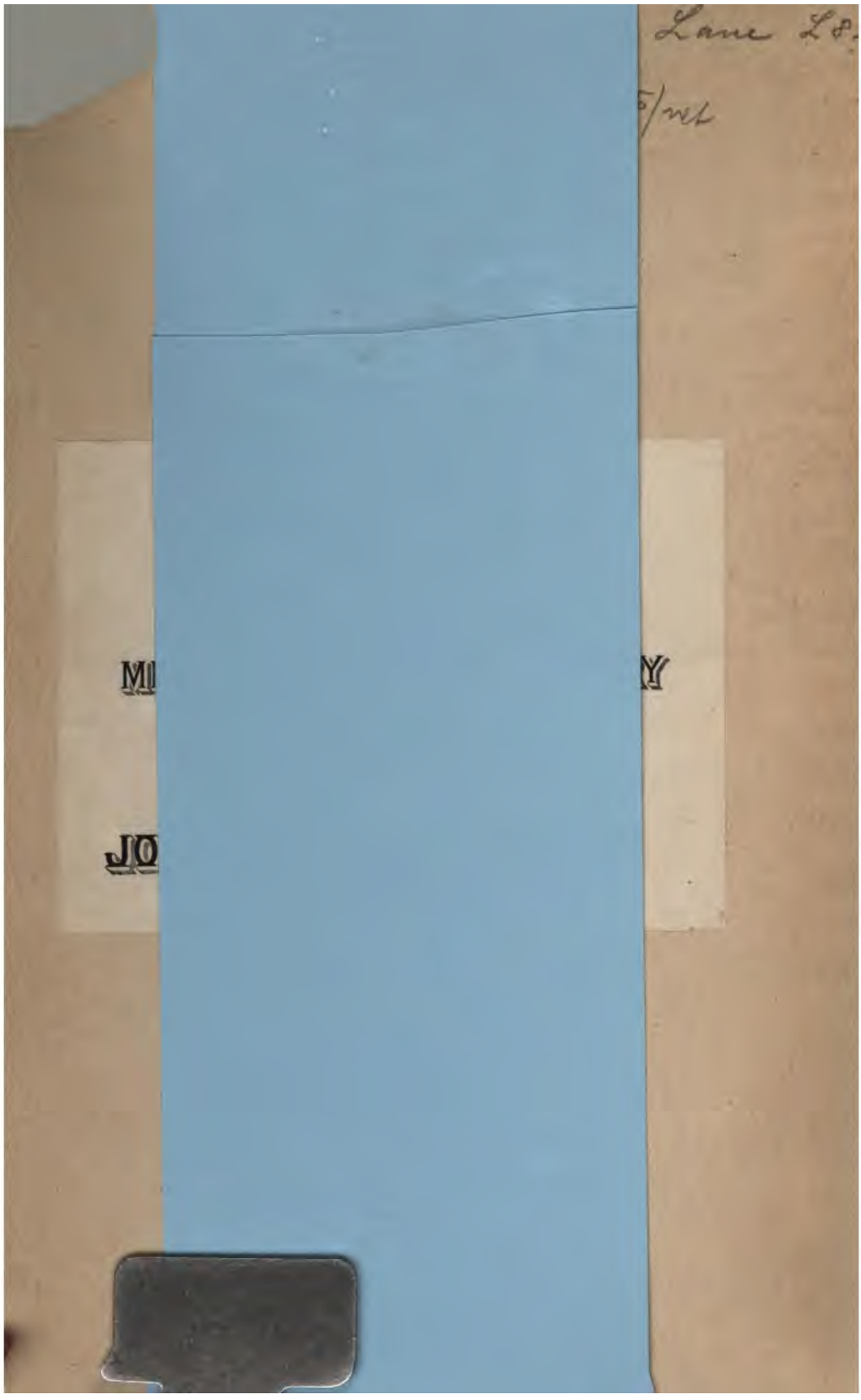
Lane Lo.
M
Y
JO

ION

ULSE

D CO.
LONDON
W YORK

MONOGRAPHS ON PHYSIOLOGY

EDITED BY

ERNEST H. STARLING, M.D., D.Sc., F.R.S., F.R.C.P.

MONOGRAPHS ON PHYSIOLOGY

EDITED BY

ERNEST H. STARLING, M.D., D.Sc., F.R.S., F.R.C.P.

8vo.

THE INVOLUNTARY NERVOUS SYSTEM. By WALTER HOLBROOK GASKELL, M.A., M.D., F.R.S. With 9 Figures. 6*s.* 6*d.* net.

THE SECRETION OF THE URINE. By ARTHUR R. CUSHNY, M.A., M.D., F.R.S. With Diagrams. 9*s.* net.

THE CONDUCTION OF THE NERVOUS IMPULSE. By KEITH LUCAS, Sc.D., F.R.S., Fellow and Lecturer of Trinity College, Cambridge. Revised by E. D. ADRIAN, M.B., M.R.C.P., Fellow of Trinity College, Cambridge. 5*s.* net.

THE PHYSIOLOGY OF REFLEX ACTION. By CHARLES SCOTT SHERRINGTON, M.A., M.D., F.R.S., F.R.C.P.

THE PHYSIOLOGICAL BASIS OF THE ACTION OF DRUGS. By H. H. DALE, M.D., F.R.S.

THE NATURE OF MUSCULAR MOVEMENT. By W. M. FLETCHER, M.A., M.D., F.R.S.

THE CEREBRAL MECHANISMS OF SPEECH. By F. W. MOTT, M.D., F.R.S., F.R.C.P.

TISSUE RESPIRATION. By C. LOVATT EVANS, D.Sc.

THE PHYSIOLOGY OF MUSCULAR EXERCISE. By F. A. BAINBRIDGE, M.B., D.Sc., F.R.C.P.

THE VASO-MOTOR SYSTEM. By W. M. BAYLISS, M.A., D.Sc., F.R.S.

LONGMANS, GREEN AND CO.

LONDON, NEW YORK, BOMBAY, CALCUTTA, AND MADRAS

THE CONDUCTION

OF THE

NERVOUS IMPULSE

BY

KEITH LUCAS, Sc.D., F.R.S.

FELLOW AND LECTURER OF TRINITY COLLEGE, CAMBRIDGE

REVISED BY

E. D. ADRIAN, M.B., M.R.C.P.

FELLOW OF TRINITY COLLEGE, CAMBRIDGE

WITH DIAGRAMS

LONGMANS, GREEN AND CO.

39 PATERNOSTER ROW, LONDON

FOURTH AVENUE & 30TH STREET, NEW YORK

BOMBAY, CALCUTTA, AND MADRAS

1917

EDITOR'S PREFACE.

In no science is the advance at any one time general. Some sections of the line are pushed forward while other parts may remain for years with little movement, until in their turn they are enabled to progress in consequence of the support afforded by the advance of the adjacent sections. The increasing number of series of monographs in different sciences is a recognition of this fact, as well as of the concentration of interest which characterizes this age of specialization.

In the present series it is intended to set out the progress of physiology in those chapters in which the forward movement is the most pronounced. Each monograph will contain an account of our knowledge of some particular branch of physiology, written by one who has himself contributed in greater or less degree to the attainment of our present position. It is hoped that by securing the help of men who are actively engaged in the advance of the subject the outlook of each monograph will be forwards rather than backwards. An exhaustive account of previous writings on the subject concerned is not aimed at, but rather an appreciation of what is worth retaining in past work, so far as this is suggestive of the paths along which future research may be fruitful of results. The

more valuable the monographs in inspiring the work of others, the greater will be the success of the series.

The present volume deals with a subject which is fundamental for the understanding of the working of the nervous system. Delayed in its appearance by the outbreak of the war, it might have been lost but for the services of Dr. Adrian, who had co-operated with Keith Lucas in many of his researches, and managed to find time, in the midst of his military duties, to edit and complete the material left behind by the author. Interesting as is the work, revealing the train of thought which guided him in his researches, it is only by reading Keith Lucas's original papers, cited in the text, that we can form some idea of his scientific personality, and appreciate the greatness of the loss science has suffered by his untimely death in the service of his country. His whole life was in his work and so the work reveals the man. In reading Lucas's papers, one is impressed in the first place with his courage. No problem is too difficult to attack—indeed the difficulty only adds zest to the undertaking. But withal there is no blind enthusiasm. One finds throughout a clearness of vision which views and evaluates in a spirit of detachment the difficulties, and a cool planning out of the best possible means to overcome them and obtain an answer to the problem set before him. His mechanical genius enabled him to attain a perfection of experimental technique which has been rarely equalled and never surpassed, without, however, warping his judgment as a biologist, or leading him to adopt the Procrustean method of fitting the phenomena of the living tissue to some mechanical schema.

The qualities, which had rendered Keith Lucas

eminent as a physiologist, are just those required in the new science which set out on the conquest of the air; and from the beginning of the war he applied all his inventive faculties to solving the practical problems which confront our aviators. How valuable his work was in this department will be disclosed later. His loss to the flying service is as great as his loss to physiology. But his work is for all time, and will serve as a sure vantage ground from which other men may carry on the quest so ably initiated by Keith Lucas.

ERNEST H. STARLING.

REVISER'S NOTE.

For one whose pride it is to regard himself as a pupil of Keith Lucas it would be out of place to speak of the loss to science which his death has entailed. However, I feel that a brief statement is necessary in regard to the part I have taken in preparing this book for the press. Keith Lucas delivered a course of seven lectures at University College, London, in the spring of 1914. The lectures were founded as a memorial to Page May, the neurologist, and Lucas chose as his subject the phenomena of conduction in nerve. He had intended to rewrite these lectures to form the present monograph, and by July, 1914, he had already finished eleven out of the thirteen chapters in the book. At the outbreak of war he offered his services to the country and was posted to the Royal Aircraft Factory at Farnborough. From that time until his death his work was concerned solely with the problems of flying, and he was killed in an aeroplane accident on 5 October, 1916. Thus the manuscript of the book was as he left it in July, 1914. To the eleven chapters which were completed I have made no alteration beyond adding one or two references to later work, though occasionally a pencilled note shows that Lucas contemplated some slight modifications in the argument. The greater part of Chapter VI. and the whole of Chapter XIII. were missing, and these I have

had to rewrite as best I could. In Chapter VI. pages 28 and 29 were already written ; for the rest I have followed the detailed notes which Lucas used in delivering the lectures, and it has been a fairly simple task to reconstruct the chapter from them. Chapter XIII. has been much more difficult to write. I am not even sure that Lucas intended to say anything about central inhibition ; a chapter on this subject is bound to contain a good deal of speculation without experimental backing, and Lucas was never fond of pure speculation for its own sake. However, some account of the possible mechanism of central conduction seems a fitting termination to the book, and Lucas left a few notes and a list of references which show the main lines of the argument he intended to develop. It has not been easy to fill in these outlines without adding a great deal of speculative matter which Lucas may have wished to avoid. In spite of this I believe the chapter does not misrepresent his views on the subject, though he may not have intended to publish these views until the experimental evidence was more complete.

My thanks are due to the Editor of the "Journal of Physiology" for permission to use many of the figures which illustrate the book.

E. D. ADRIAN.

ALDERSHOT, *June*, 1917.

CONTENTS.

CHAPTER I.

INTRODUCTION.

YOUR invitation to deliver these lectures came to me as a pleasure of quite a special kind. The work of Page May, whose name the lectureship commemorates, and the subjects chosen by my predecessors combine in associating these lectures with the study of the central nervous system. I am in no sense fit to carry on that torch, for my own interest in Neurology has lain outside the centres, has been concerned only with the happenings in peripheral nerve. And yet I have eagerly accepted your invitation, because I am convinced that the study of conduction in peripheral nerve holds the key to some of the fundamental problems of the central nervous system.

In one sense it has been obvious from the first that the student of the central nervous system has common interest with the investigator of peripheral nerve. One of the chief concerns of the latter is to discover the physico-chemical change which is the basis of conduction; and, as Sherrington has said, "the intimate nature of conduction is a problem coextensive with the existence of nerve cells, and enters into every question regarding the specific reactions of the nervous system". But when the student of conduction in peripheral nerve leaves aside the physico-chemical theory of the nervous impulse and attempts merely to investigate in detail the phenomena of conduction, then it has seemed to many that his work becomes academic, and loses touch with the great human interests of the nervous system. Conduction in peripheral nerves is a rigid affair, seeming to lack just those features, Inhibition, Summation, Rhythm, After-discharge, which give to central conduction its flexibility and its means of adaptation to specific ends.

There is no need to press this point further; the differences between peripheral conduction and conduction in the reflex arc form a common theme for the academic essay of the elementary student.

What is the meaning of these differences? Are we to suppose that the central nervous system uses some process different from that which is the basis of conduction in peripheral nerves, or is it more probable that the apparent differences rest only on our ignorance of the elementary facts of the conduction process? If we had a fuller knowledge of conduction as it occurs in peripheral nerve, should we not see Inhibition, Summation, and After-discharge as the natural and inevitable consequences of that one conduction process working under conditions of varying complexity? Physiologists have answered this question in both ways. McDougall and v. Uexküll have each put forward hypotheses which account for the phenomena of Inhibition by postulating a process unknown to the student of nervous conduction, namely, the passage along nervous paths of a something which can stay and accumulate in one part or another of the nervous system. Verworn and his school have taken the opposite line and attempted to account for the central phenomena in terms of the elementary properties revealed by experiment on the simple excitable tissues.

Which method are we to follow? If I might make a suggestion it would be this: that we should inquire first with all care whether the elementary phenomena of conduction, as they are to be seen in the simple motor nerve and muscle, can give a satisfactory basis for the understanding of central phenomena; if they cannot, and in that case only, we shall be forced to postulate some new process peculiar to the central nervous system. But if this is to be our task in these lectures, shall we not be treading old ground, seeing that Verworn and Fröhlich have already given us a scheme which claims to explain Inhibition and Summation in terms of the elementary facts of conduction? I would be the first to acknowledge the debt which Neurology owes to these workers for the stimulus

which they have given to progress in this direction. Their account of central phenomena is, however, as I believe, founded on insufficient analysis of the elementary process itself, and leads therefore to imperfect synthesis. We shall not build securely unless we start by examining with a critical judgment the foundation of our knowledge of conduction. This knowledge must constitute what I would venture to call the elements of Neurology, the analytical basis from which we may proceed to reconstruct the complex phenomena of conduction in the reflex arc. It will therefore be my first aim to lay before you as far as possible the experimental evidence upon which our fundamental knowledge of conduction rests, and to sift what is established from what is guessed. This done, we shall return with more confidence to inquire whether conduction in the central nervous system calls for the postulation of any principle which the elementary analysis has not revealed.

In considering the elementary process of conduction I have left many points untouched ; I have not dealt with the relation between the mechanism of excitation and of conduction, the relation of the impulse to the electric response, the rate of conduction, the effect of changes in the fluid surrounding the nerve. All these are part of the classical " muscle and nerve " physiology, and they are of great importance when we are investigating the exact nature of the nervous impulse, but for the present we are not concerned with this. The question I wish to discuss is not why the nerve conducts, but how it conducts, and how far the phenomena of conduction in a peripheral nerve may be made the basis of the understanding of conduction in the central nervous system.

CHAPTER II.

THE MEASUREMENT OF THE NERVOUS IMPULSE.

THE first problem of conduction is whether the nervous impulse is a variable quantity, or whether in each unit fibre of the nervous system it is always of like strength. The investigation of this question is one of singular difficulty because the impulse is so intangible. If we stimulate a motor nerve and record the contraction of the muscle innervated, we conclude that a nervous impulse has passed from the seat of excitation to the muscle; but how are we to come to closer contact with that nervous impulse, to learn something more about it than the mere fact that it has or has not passed along the nerve? That we can measure its rate of passage we all know, but that does not help us much; we want to know how the impulse varies in intensity, whether it is stronger if the stimulus is stronger, whether it is weakened by passing a region of partial obstruction such as the junctional tissue between nerve and muscle. It is only when we can measure the nervous impulse that we begin to learn the elements of conduction.

It might appear at first sight that we could learn something of the intensity of the impulse from the magnitude of the effect which it produces. If a larger contraction results from stimulation of the motor nerve we might infer an increase in the intensity of the nervous impulse. This method is open to two fatal objections. Any nerve with which we can experiment is comprised of many unit fibres, and a larger contraction might result with equal probability either from an increase of intensity in each nerve fibre, or from an increase in the number of fibres brought into action. And even if this difficulty were overcome by the use of a single nerve fibre, there would remain the objection that

we should be measuring the intensity of the impulse in terms of the magnitude of contraction, whereas we have no knowledge whatever of the function relating these quantities. If we turn to a process which seems more intimately connected with conduction, the electric response of nerve, and attempt, as many physiologists have done, to measure the nervous impulse in terms of the magnitude of the accompanying electric response, we are still no nearer to the truth; here again an alteration in the number of fibres may be mistaken for an alteration in intensity. In fact every attempt of this kind is doomed to failure, and there remains, so far as I am aware, but one method by which the nervous impulse can be measured. This method depends upon a certain fundamental property of conduction, the proof of which must now occupy our attention for a while.

As far back as 1872 Grünhagen[1] made what has been called the "gas-chamber" experiment on nerve. He took a nerve-muscle preparation and passed a portion of the nerve through a glass chamber, so that that portion could be exposed to the action of carbon-dioxide, while the parts above and below were in the air. He then tested the strength of stimulus required to cause a contraction of the muscle when applied either outside or inside the gas-chamber. Szpilman and Luchsinger[2] repeating this experiment nine years later, found that if the narcotic was allowed to act for a long time a stage was reached in which a stimulus would cause a contraction of the muscle if applied to the part of the nerve within the gas-chamber, whereas it would cause no contraction if applied outside the chamber in such a position that the nervous impulse which it set up must traverse the whole of the gas-chamber on its way to the muscle. The explanation which they offered of this fact was that the impulse on its passage through the narcotised part of the nerve became gradually less intense, and failed entirely if the length of narcotised nerve to be traversed was sufficient; thus the "outside" stimulus caused no contraction of the muscle because the

[1] Grünhagen, "Arch. f. d. ges. Physiol.," vi. p. 157, 1872.
[2] Szpilman and Luchsinger, "Arch. f. d. ges. Physiol.," xxiv. p. 347, 1881.

nervous impulse which it started had to face a longer stretch of narcotised nerve than did that set up by the "inside" stimulus.

This suggestion seems to have been neglected by later workers; eighteen years passed before Werigo [1] suggested to his pupil Rajmist that he should determine experimentally what influence the length of nerve narcotised had on the depth of narcosis required to abolish conduction. Rajmist found that the depth of narcosis required became continuously less as the length of nerve exposed to the narcotic was made greater. This result is obviously in complete agreement with the hypothesis of Szpilman and Luchsinger; the nervous impulse would fall off less rapidly under the weaker narcotic, and would therefore reach extinction only after a longer passage through the narcotised nerve. Werigo, however, interpreted it differently, and their hypothesis seems to have lain dormant until Fröhlich [2]

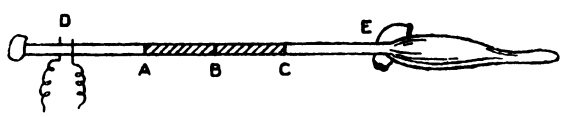

FIG. 1.

repeated and extended Rajmist's observations, and suggested afresh that the only reasonable explanation of the facts was to be found in the continuous decrement of the impulse during its passage along narcotised nerve.

The difference between continuous decrement and sudden extinction without previous decrease is one of fundamental importance for our knowledge of conduction. If the experiments really prove a continuous decrement, then one of the factors which we shall have to consider in conduction will be the intensity of the nervous impulse; if not, it is possible that the impulse may be of invariable intensity, all or none. We must examine the evidence more closely.

The experimental fact is that if a given length of nerve AB (Fig. 1) acted on by a given narcotic for a given length of time

[1] Werigo, "Arch. f. d. ges. Physiol.," lxxvi. p. 552, 1899.
[2] Fröhlich, "Ztschr. f. allg. Physiol.," iii. p. 148, 1904.

allows a nervous impulse set up at D to reach E, that nervous impulse may fail to reach E if the total length of narcotised nerve is increased from AB to AC. This result holds good when the length BC is less than AB, so that BC alone could not extinguish the impulse. It is inferred that the impulse in its passage through AB undergoes some change which renders it less able to be conducted through BC. Thus when the impulse arrives at B it is not extinguished and yet is reduced in its ability to be conducted. Do these facts give proof that the impulse in a single fibre undergoes change, or may they be explained by the supposition that on its arrival at B the impulse has been completely extinguished in some fibres, whereas in the remainder it is entirely unchanged? A single isolated observation of the kind described above might be explained on the ground that in its passage along AB the impulse, though possibly extinguished in some fibres, was wholly unchanged in the remainder, and that in the latter fibres it was extinguished in its passage along BC. This explanation becomes untenable when we consider the regularity with which the phenomenon occurs, for it demands the supposition that whenever we increase the length of the narcotised nerve the action of the narcotic happens to be stronger in the added portion than it was in the original portion. Such a perverse supposition need not be considered beside the simple view that the added length increases an effect already produced in some degree by the original length.

On this view then the nervous impulse undergoes a change which increases with the distance travelled through the narcotised nerve. This change we may, if we will, speak of as a reduction in strength or intensity; but we ought to have clearly before our minds that the actual change observed is a reduction of the ability to be conducted through narcotised nerve. The fundamental fact is that the further an impulse has been conducted through narcotised nerve, the shorter is the distance which it is able to be conducted before complete extinction. It is as though a man were to start on a march across a desert without supplies. The further he had marched the less would be the distance which

he could still cover without dying. We might then say that his strength decreased continuously as he travelled, and estimate his strength at any stage of the journey in terms of the length of desert march which still remained before death should overtake him.

I have entered in some detail into this question of the decrement of the impulse, as it is called, because it proves the essential point that the nervous impulse is a variable quantity, and because it is the basis of our only method of measurement. The principles of that method will already be evident. If we wish to measure the intensity of a nervous impulse we can set it to face a tract of nerve in which it will undergo a decrement, and determine how far it is able to travel before it is extinguished. The measure of intensity so obtained is in terms of the ability of the impulse to travel, just as the strength of the explorer may be measured in terms of the distance he can cover before he is exhausted. It is true that we cannot translate this intensity into any quantity of physical or chemical meaning in the present state of our knowledge, but we can learn just the one point which is important to the study of conduction, namely, the chance that an impulse has of being conducted successfully. The details of this method need not trouble us now. There will be opportunity enough for considering the technique when we come to examine the various conditions by which the nervous impulse is modified.

CHAPTER III.

THE EFFECT OF STRENGTH OF STIMULUS ON THE IMPULSE.

SINCE the nervous impulse is found to be of variable intensity the central problem of our inquiry is to determine how far it is modified by various conditions. There are of course hosts of drugs and abnormal conditions which if applied to nerve will alter its ability to conduct, but for the most part these lie outside the scope of the present problem; they are of use as technical means in research, and their action may help in elaborating a physico-chemical theory of conduction, but it is no immediate part of the present inquiry to catalogue their effects. The knowledge which we need is of the normal conditions by which the impulse may be modified in its course within the body. If the range of investigation is limited in this way, the possible causes of modification become comparatively few. There is the antecedent history of the impulse; it will be necessary to determine whether two impulses which pass along the same tract of nerve can be of different intensity because they have been launched into it under different conditions, one having been initiated by a weaker external stimulus, or having passed through a region of decrement. Then there is the question of the momentary condition of the nerve; is an impulse modified in strength if it follows another before the disturbance due to its predecessor has subsided? Lastly, does the impulse normally pass throughout the nervous system without decrement, or are there regions in which conduction is normally imperfect?

The question whether the intensity of a nervous impulse depends at all on its previous history or only on the immediate condition of the conductor which carries it has been investigated by two methods. One is to provoke the nervous impulse by

stimuli of different strengths and to see whether it then has different intensities; the other is to reduce it to subnormal intensity by passage through a region of impaired conduction, and to ascertain whether it regains full intensity when it has passed into normal nerve.

The chief interest of the problem has centred round the question whether the nervous system is able to effect a graded activity in the muscles and other end organs by sending to them impulses of different intensity. It was long thought that the increase of contraction produced in a muscle by the application of stronger artificial stimuli to its motor nerve was due to the provocation of stronger impulses in the nerve.[1] Gotch[2] was the first to throw doubt on this interpretation. He pointed out that the submaximal contraction of a muscle or the submaximal electric response of a nerve in answer to a weak stimulus resembles the effect produced by a maximal excitation of a few of the fibres, since the time-relations of the submaximal effect do not differ from those of the maximal effect. He suggested that the grading of activity might be effected by a variation not of intensity of the process in each fibre, but of the number of fibres engaged. This work weakened the grounds for postulating a variable intensity of the nervous impulse in answer to varying stimuli, but did not directly disprove such a possibility. The same may be said of some experiments which I made by a different method.[3] I showed that if the cutaneous dorsi muscle of the frog is excited through its motor nerve, which does not contain more than ten nerve fibres, increase of the stimulus by many small successive steps leads to an increase of the muscular contraction in a few large steps. The number of steps was always less than the number of nerve fibres in the motor nerve, and when the strength of stimulus was sufficient to cause the contraction to rise by one step, a further increase of strength

[1] Fick, "Gesam. Schriften," iii. p. 109, 1864; Wertheim-Salomonson, "Arch. f. d. ges. Physiol.," c. p. 455, 1903.

[2] Gotch, "Journ. of Physiol.," xxviii. p. 395, 1902.

[3] Keith Lucas, "Journ. of Physiol.," xxxviii. p. 113, 1909.

did not cause a further increase of contraction until a new step was reached. This fact means apparently that once the strength of stimulus is sufficient to excite a given nerve fibre, the muscle fibres innervated by that nerve fibre respond as fully as they can. If this is the case the necessity for postulating a variable intensity of the impulses in the motor nerve disappears. But again the possibility of variation is not disproved.

Symes and Veley[1] first dealt with the problem by a direct method. They treated a motor nerve locally with cocaine, stovaine, and other anæsthetics, and found that when a stimulus of fully maximal strength applied above the anæsthetised region failed to cause a contraction of the muscle, no contraction resulted if the strength of the stimulus was made several hundred times greater. This observation is an example of the method of measuring the nervous impulse which we have already considered. It is found that an anæsthetic acting for a certain time just extinguishes the impulse which tries to pass through the affected region; the stimulus is made much stronger and still the impulse does not pass through. It follows that the impulse set up by the stronger stimulus is not conducted further through the region of decrement than that set up by the weaker stimulus. The exact terms in which Symes and Veley expressed this result was that "the amplitude of a nervous impulse is, within normal limits of stimulation, substantially maximal or zero".

The same proof that the strength of the stimulus does not influence the intensity of the impulse in nerve was brought forward by Verworn[2] a short time afterwards. He was apparently not aware of the work of Symes and Veley, and based his conclusions on similar observations made by Fröhlich. Veszi[3] also discussed the matter in a paper which appeared from Verworn's laboratory at about the same time. At Verworn's suggestion Lodholtz[4] repeated the experiments and obtained

[1] Symes and Veley, "Proc. Roy. Soc. B.," lxxxiii. p. 421, 1910.

[2] Silliman Lectures, University of Yale, Oct. 1911. Published as "Irritability," Yale University Press, 1913. See particularly p. 140 of the latter work.

[3] Veszi, "Ztschr. f. allg. Physiol.," xiii. p. 321, 1912.

[4] Lodholtz, "Ztschr. f. allg. Physiol.," xv. p. 269, 1913.

results which are of some interest. It will be recalled that Symes and Veley used as their weakest stimuli currents which were fully maximal; Fröhlich and Lodholtz, however, always tested what was the weakest stimulus which would suffice to send an impulse through the narcotised tract of nerve. Lodholtz found that it was by no means always true that when a current which had just sufficed to send an impulse through the narcotised tract failed to do so, a stronger current also failed. In about half the cases observed when first the weak stimulus failed a stronger stimulus was successful. The important question then arose whether this meant that the stronger stimulus set up an impulse which was better conducted than that set up by a weaker stimulus. Lodholtz was of opinion that this was not so, and suggested the alternative explanation that in these cases the nerve fibres which were excited by the weak stimulus chanced to be narcotised more rapidly than others, so that when the stimulus was strengthened it brought into action fibres which were not yet narcotised so deeply, and in these fibres the impulse was able to pass through the narcotised tract without extinction. The suggestion was certainly a probable one, but lacked proof. Adrian[1] took this point up experimentally and confirmed Lodholtz's suggestion. He showed that if the stimulus used was the weakest which would just excite all the fibres of the nerve, then at the moment when the nerve first failed to transmit an impulse in any of its fibres owing to the action of the narcotic, it failed whether the stimulus was of the strength which had only just sufficed to excite the fibres or was of much greater strength. To this observation there were no exceptions. It is well to notice the precise significance of this experiment. It is apparently a matter of chance whether the fibres in which conduction is first suspended are or are not those which require the strongest current for their minimal excitation. Since the current used is the weakest possible only for those which are the least excitable, it will often happen that the fibres in which conduction

[1] Adrian, "Journ. of Physiol.," xlvii. p. 460, 1914.

is first suspended are being stimulated with a current considerably above their threshold. However, eventually those fibres which are least excitable will also become unable to conduct. In these fibres the stimulus is only just strong enough to excite, and the experiment proves that an increase in the strength of the stimulus causes no better conduction in any of the fibres during any stage of the process of narcotisation. Thus there is definite evidence that in the least excitable fibres the impulse is no better conducted when the stimulus is increased from the least strength which will excite at all to a strength much greater. This is the point which the experiments of Symes and Veley did not show at all, and those of Lodholtz did not prove with certainty.

I fear that the argument of these experiments becomes somewhat complex. Such is, however, the characteristic of much experimental work on the excitable tissues. The experiments are often easily made, even with a considerable degree of accuracy; it is in their interpretation that the real difficulty begins. And this difficulty arises again and again from the same cause, that nerves and muscles are not units, but each composed of many fibres.

In the present problem, however, there is a point of interpretation to be faced on a different level. The experiments show, without doubt as I believe, that when a stimulus of greater strength than the minimal is applied to a nerve, the resulting nervous impulse is no more intense, as measured by its ability to be conducted, than one set up by a minimal stimulus. But is it true that when a strong stimulus is applied to a nerve the nervous impulse which follows was set up by a strong stimulus? Consider what happens at the seat of excitation. The electric current, if only just strong enough to excite at all, excites in the cathodic region at the point where the current passing out of the nerve is of highest density. If now a stronger current is used the part of the cathodic region within which the current is dense enough to excite will be more extended. Over the whole of this region the conditions necessary for starting a nervous impulse

will presumably be realised. But it will be only from the peripheral part of this region that a nervous impulse will be conducted away, since any impulse which attempts to follow it from the inner part of the excited region will be blocked by the refractory period which the impulse of peripheral origin leaves behind. Now the impulse set up in the periphery is set up by a current only just strong enough to excite at all (this in fact is the meaning of the periphery, the outermost point at which the current is strong enough to excite). It follows that whatever strength of current is applied to the nerve, the impulse which travels away has been set up by a minimal current.

This point was first raised by Adrian in a footnote to the paper in which he dealt with the interpretation of Lodholtz's experiments.[1] If such a conception of the action of strong electric stimuli is correct (and I see no escape from that conclusion), it follows that all attempts to determine the effect of strong stimuli on the nervous impulse have failed. We have in fact no case in which an impulse has been provoked by any stimulus other than the weakest possible. This line of work therefore leaves us in the dark on the question whether the impulse transmitted along a nerve depends for its intensity on the conditions of its initiation. The only outcome of the inquiry is to strengthen the evidence which has led us to conclude that, when a motor nerve is artificially excited with stimuli of varying strengths, the graded contraction of the muscle results solely from variation in the number of fibres brought into action. For if the nerve can only be excited by minimal stimuli the number of fibres stimulated is the only variable which can be introduced by a change in the strength of the stimulus. The proof that so much grading can be accomplished by this method acting alone justifies the view that the postulation of any other method is at least unnecessary until proof be found of its existence.

It must be remembered that the experimental work on which this view depends has been confined to the motor nerves

[1] Adrian, loc. cit.

of the frog, and it is perhaps an unjustified assumption to extend it to cover sensory nerves as well. Both Graham Brown[1] and Lapicque[2] have shown in reflex conduction a relation between stimulus and response which is at first sight difficult to reconcile with the view that the intensity of the impulse passing up the afferent nerve fibres does not vary with the strength of the stimulus which set it up. Again, a grading which depends simply on the number of fibres involved seems inadequate to explain the wide variations in the intensity of the sensations we experience, particularly in the case of light and sound. Forbes[3] has suggested that the reflex response may be graded both by the number of sensory fibres stimulated and also by the number of impulses set up by each stimulus, and he has given good reasons for the view that a single strong stimulus may lead to several distinct impulses in the nerve fibre. This would account satisfactorily for most of the observations which seem to show a relation between the strength of stimulus and intensity of impulse in sensory nerves. It is certainly a pity that we cannot experiment as easily with sensory nerves as we can with motor, but it is unlikely that the processes of conduction are radically different in the two. In any case if the impulse in a sensory nerve is followed, as in a motor nerve, by a refractory period, it is difficult to avoid the conclusion that the effective stimulation is always one of minimal strength whatever the strength of the stimulating current may have been.

We must therefore confess frankly that so far as this line of evidence is concerned, we do not know whether a nerve in its normal situation does, or even can, transmit impulses which differ in intensity because they have been differently launched. Nor is it easy to see how the method of varying stimuli is to solve the problem in the future. Whatever the nature of the stimulus used, whether electrical, mechanical, or chemical, there is always some spread of the condition which

[1] Graham Brown, "Proc. Roy. Soc. B.," lxxxvii. p. 132, 1913.
[2] Lapicque, "C. R. Soc. de Biol.," lxxii. p. 871, 1912.
[3] Forbes, "Amer. Journ. Physiol.," xxxix. p. 172, 1915.

serves as a stimulus when that change is made more than minimal. And there will always be a peripheral zone of minimal change from which the impulse will presumably take its origin. So we are driven back to the other method of experiment already mentioned, that which reduces a nervous impulse by a local impairment of conduction and then examines its intensity after it has passed out into normal nerve.

CHAPTER IV.

THE RECOVERY OF A NERVOUS IMPULSE WHICH HAS BEEN REDUCED.

THE first observations on this point were made by Boruttau.[1] He expressed the view that if the local cooling of a nerve is sufficient to offer a difficulty of propagation, then the impulse on emerging into normal nerve again does not recover its normal size. Boruttau and Fröhlich[2] studied the question by narcotising a nerve locally with carbon-dioxide and examining the electric response both within and without the narcotised tract. They found that the electric response outside a narcotised tract in which it has been reduced maintains an intensity less than normal. This fact, however, gives no proof that in each fibre the impulse remains small on emerging from a region in which it has suffered decrement. As we saw when considering the method of measuring the nervous impulse, the electric response of a nerve may be reduced either because it is smaller in each nerve fibre, or because it is present in a smaller number of fibres. In these experiments it is likely that narcosis will not proceed at the same rate in all the fibres of the nerve, so that, even if the electric response recovers its full size in each fibre which succeeds in passing the impulse right through the narcotised region, we should expect at any late stage of narcosis that the nervous impulse will be extinguished completely in some fibres, and consequently the electric response of the nerve below the narcotised tract will be reduced.

This source of error can be avoided only if the nervous impulse is measured in terms of its ability to be conducted. Adrian has applied this method, and his results form really

[1] Boruttau, "Arch. f. d. ges. Physiol.," lxv. p. 7, 1896.

[2] Boruttau and Fröhlich, "Arch. f. d. ges. Physiol.," cv. p. 444, 1904.

the only definite experimental evidence we have on the question.

The principle of Adrian's method[1] was to reduce the nervous impulse to subnormal intensity, and then to pass it into normal nerve and determine whether it there became normal in its ability to be conducted. We have already seen the evidence which tells us that the impulse is not extinguished instantaneously at one point of its passage through a narcotised tract of nerve, but is rendered progressively less able to be conducted before it finally reaches extinction. It is on this fact which Adrian relied in order to reduce the impulse artificially to subnormal intensity. Suppose a nerve to be narcotised over the length AB (Fig. 2) to such an extent that a nervous impulse started at I just fails to pass through it. We may then represent the change in the nervous impulse diagrammatically as in the figure, where AC is

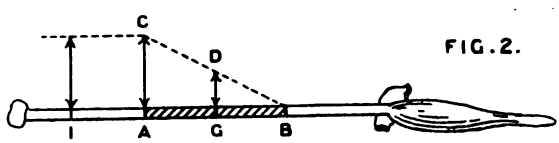

FIG. 2.

a measure of the intensity of the nervous impulse as it enters the narcotised tract, GD represents its reduced intensity after travelling half-way along the tract, and near B it is shown to be extinguished completely just before it has been able to reach the normal nerve again. Now suppose that the impulse when reduced to the intensity GD had been allowed to enter normal nerve again instead of going on in narcotised nerve, would it have recovered the intensity AC, or would it have remained at the value GD? Clearly this point may be tested experimentally if we divide the narcotised tract AB into two halves AG and G^1B and insert the length of normal nerve GG^1 between them. Then if the impulse on entering the normal tract does not recover, it will be extinguished as before by its passage through the remaining piece of narcotised nerve, as Fig. 3 shows. If this diagram represents the facts, the same degree of narcosis will

[1] Adrian, "Journ. of Physiol.," xlv. p. 389, 1912.

evidently suffice to extinguish the impulse whether the narcotised tract is continuous or broken into the sections AG and G^1B. But suppose that the impulse does recover when it passes into the normal tract GG^1, then we shall have the conditions shown in Fig. 4, and the original degree of narcosis will by no means extinguish the impulse when the narcotised tract is divided.

This is the argument of Adrian's experiments, and you will notice that the intensity of the disturbance which has emerged into normal nerve is compared with that which is still in nar-

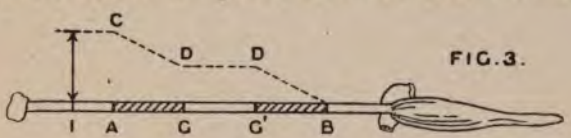

FIG. 3.

cotised nerve by determining whether the same length of narcotised nerve is required to extinguish both. If I may recall for a moment the analogy of the traveller who started across the desert without supplies, the counterpart of the present experiment would be that he should find in the middle of the desert an oasis where supplies were in plenty. The problem is whether his crossing the second half of the desert would thereby be made easier. The answer to this problem as it concerns the nervous impulse is given quite definitely by Adrian's experiments. He

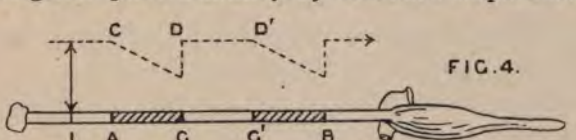

FIG. 4.

passed alcohol vapour from a common source simultaneously over two sciatic nerves taken from the same frog. In one nerve the alcohol affected a length of 9 mm. In the other the stream of vapour was divided and affected two lengths each of 4·5 mm., between which there was about 10 mm. of normal nerve. The experimental arrangement is reproduced in Fig. 5.

The preparation X has its nerve passing through the two alcohol chambers A and B, each 4·5 mm. wide. This nerve can be excited either at I or at II, so that the impulse will have to pass either one or both of the narcotising chambers on its

way to the muscle. The nerve of the preparation Y passes through the chamber C, 9 mm. wide, and can be excited at III. The preparation Z is a control, whose nerve passes through one narcotising chamber of 4·5 mm. The alcohol vapour is drawn through all the chambers from one bottle by the branching glass tube shown at the top of the diagram.

If the nervous impulse does not recover on emerging from a region of decrement into normal nerve, then the effect of the chambers A and B will be equal to that of the chamber C, so that conduction from the electrodes II should fail at the same

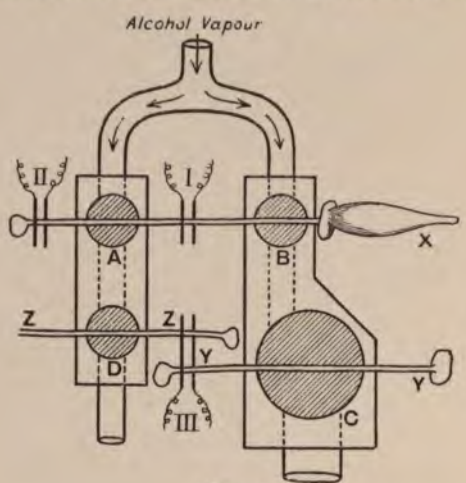

FIG. 5.

stage of narcosis at which conduction fails from the electrodes III. On the other hand, if the impulse recovers on emerging into normal nerve, then conduction from III should fail at a stage of narcosis which is insufficient to suspend conduction from II. Moreover, since the chambers A and B are equal, if the impulse recovers on emerging from A, then conduction should fail at the same stage of narcosis whether the stimulus is applied at II or at I, that is whether the impulse has to pass both the chambers A and B or only the one.

Adrian used as a measure of the depth of narcosis required to extinguish the impulse in each case the time of passage of the alcohol vapour which was necessary. This method is a con-

venient one, since the action of the narcotic can be made to proceed quite slowly if its strength is rightly chosen. The results of this experiment are shown in the table below, and you will see at once that they are in complete agreement with our forecast of what would happen if the nervous impulse recovered its normal size on emerging from the region of decrement. In every case the conduction is suspended by the 9 mm. chamber in a shorter time than by the joint action of the two smaller chambers.

TABLE I.—ALCOHOL AS NARCOTIC.

Experiment.	Time to Failure of Conduction.		
	Preparation X. Disturbance Passes.		Preparation Y. Disturbance Passes.
	B only (4·5 mm.)	A and B (4·5 + 4·5 mm.)	C only (9·0 mm.)
1	10 minutes	10 minutes	6 minutes
2	10½ ,,	10 ,,	6½ ,,
3	13 ,,	13 ,,	7 ,,
4	12½ ,,	12 ,,	8 ,,
5	16 ,,	16 ,,	8½ ,,
6	18½ ,,	17 ,,	10 ,,
7	24 ,,	24 ,,	16 ,,
8	26 ,,	26 ,,	17 ,,
9	26½ ,,	25 ,,	17½ ,,
10	34½ ,,	33 ,,	19 ,,

The mean values for all the experiments are, for the suspension of conduction by the one large chamber 11½ minutes, and by the two small chambers 19 minutes. Also the other prediction is verified, namely, that the time required to suspend conduction through one of the small chambers agrees closely with that required when the impulse has to pass the two in succession. In half the experiments the time required with the one chamber only is slightly longer than that with the two, but this is only a small difference of the order to be expected from inequalities in the lengths of the chambers.

It is impossible to enter here into all the control experiments which were used to examine possible sources of error in these observations. I will, however, put before you what is often the most valuable evidence, a series of observations made by a different method. In these Adrian used morphia in a solution

of weak acid as a narcotic; there was no circulation of the narcotic, but each nerve passed through baths of morphia of appropriate lengths. These experiments reproduce all the features of those made with alcohol, and are not subject to the errors which are sometimes introduced into narcotic vapour experiments by slight air-leaks in the apparatus.

TABLE II.—MORPHIA SOLUTION AS NARCOTIC.

Experiment.	Time to Failure of Conduction.	
	Preparation X. Disturbance Passes.	Preparation Y. Disturbance Passes.
	4·5 mm. only / 4·5 + 4·5 mm.	9·0 mm.
21	21 minutes / 20 minutes	12 minutes
22	26 „ / 26 „	15 „
23	18½ „ / 18 „	13 „
24	33½ „ / 32 „	28 „
25	16 „ / 16 „	10 „
	Disturbance Passes.	Disturbance Passes.
	9 mm. only / 9 + 9 mm.	18 mm.
26	15 minutes / 15 minutes	9 minutes
27	10 „ / 9½ „	6 „
28	17 „ / 17 „	11 „

The fact which these experiments seem to me to establish is that an impulse which has been reduced in its ability of conduction by passage through a region of decrement recovers that ability in full when it emerges into a tract of normal nerve. This conclusion may appear to be a limited one, and one which perhaps fails in itself to answer directly the question whether a nerve cell in the central nervous system is able to send out impulses of graded intensity to the effector organs of the body. It shows that if the impulse sent into normal nerve is of a kind less able to face extinction than the largest impulse which our artificial stimuli can provoke, there will be a recovery up to the normal level in the nerve trunk. But is it not possible that all the impulses which our artificial stimuli provoke are smaller than those which the central cell can send out, and that gradation may occur within that higher level? I think the answer to this question is contained in certain inferences which may legitimately be drawn from Adrian's experiments.

CHAPTER V.

THE CLASS OF DISTURBANCE TO WHICH THE IMPULSE BELONGS.

A DISTURBANCE, such as the nervous impulse, which progresses in space must derive the energy of its progression from some source; and we can divide such changes as we know into two main classes according to the source from which their energy is derived. One class will consist of those changes which are dependent on the energy supplied to them at their start. An example of this kind is a sound wave or any strain in an elastic medium which depends for its progression on the energy of the blow by which it was initiated. A sound wave will soon lose its initial energy if the medium in which it progresses is imperfectly elastic, because the medium will be heated in its deformation. Suppose a sound wave travelling through air and then encountering a tract of treacle. In its passage through the treacle it will lose its energy more rapidly than in its passage through the air, but on emerging into the air again it will have suffered permanent loss, and will not recover the energy which it had before it entered the treacle. A second class of progressive disturbance is one which depends for its progression on the energy supplied locally by the disturbance itself. An example of this type is the firing of a train of gunpowder, where the liberation of energy by the chemical change of firing at one point raises the temperature sufficiently to cause the same change at the next point. Suppose that the gunpowder is damp in part of the train; in this part the heat liberated will be partly used in evaporating water, and the temperature rise will be less, so that the progress of the chemical change may even be interrupted; but if the firing does just succeed in passing the

damp part, the progress of the change in the dry part beyond will be just the same as though the whole train had been dry.

The recovery of the nervous impulse after its reduction in a narcotised tract of nerve suggests that the disturbance transmitted may be of the second type, depending for its progression on the local supply of energy from a source distributed along the nerve-fibre. This view might seem to be opposed by the failure of physiologists to detect any rise of temperature in a nerve which is conducting impulses. We must remember, however, the limits of such observations. Hill[1] has found that when a nerve is placed on a thermopile connected with a galvanometer the thermopile shows unaccountable changes of temperature of the order of 7×10^{-6} of a degree Centigrade. These changes of temperature are not removed by the most careful shielding of the apparatus, so that it is impossible to tell whether the passage of a nervous impulse does or does not produce changes of temperature smaller than these; it can only be asserted that the passage of some 600 impulses does not produce changes which are larger. It is true that these observations compel the supposition that the energy liberated in the passage of the nervous impulse must be very little, but that some energy is liberated our knowledge of the oxygen use of nerve confirms.

The evidence that nerve uses oxygen in the transmission of the impulse must not be confused with the observation that nerve ceases to transmit the impulse if oxygen is removed. Baeyer[2] first proved the latter point by his experiments on nerve in nitrogen, and Fillié[3] showed the same to be true when the nerve was placed in physiological salt solution free from oxygen. The experiments of Fillié are important as showing that the loss of conductivity observed by Baeyer was not due to an accumulation of products of activity in the nerve; they also gave a definite minimum value to the oxygen concentration at which the nerve will conduct, namely, between 0·1 and 0·3 mg.

[1] Hill, "Journ. of Physiol.," xliii. p. 433, 1912.
[2] Baeyer, "Ztschr. f. allg. Physiol.," ii. p. 169, 1903.
[3] Fillié, "Ztschr. f. allg. Physiol.," viii. p. 492, 1908.

of oxygen per litre. These results, important as they are, do not prove that oxygen is used in the transmission of the impulse. If the air in a telephone exchange were replaced by nitrogen, the subscribers would soon be unable to obtain a call, but it does not follow that the passage of electric currents uses oxygen. The oxygen may be needed in nerve for the maintenance of the mechanism in working order. The observations of Thörner,[1] however, have more bearing on the point. He showed that whereas the continued passage of impulses down a nerve in air fails to render the nerve less excitable, when a nerve is placed in an atmosphere of nitrogen it loses its excitability more rapidly if impulses are passing down it than if they are not. This observation raises a strong probability that the impulses passing down the nerve lead to a more rapid use of the small supply of oxygen that the nerve contains. There is evidence of another kind which appears to confirm this.

Waller[2] long ago suggested that the passage of a nervous impulse was accompanied by the output of carbon-dioxide. His evidence was that when impulses were sent repeatedly down a nerve the character of the electric response was changed in precisely the same way as it was if a little carbon-dioxide were added to the nerve. As Waller said recently in his Californian Lectures,[3] "If, after all, you think it is not carbonic acid but 'something else' that produces effects like those of carbonic acid, I am quite satisfied". His view has now been confirmed by the striking experiments of Shiro Tashiro.[4] He has shown by a beautiful micro-chemical technique that it is possible not only to observe but actually to measure the carbon-dioxide produced in the metabolism of surviving nerve, and he finds that the output of carbon-dioxide is increased about 2·5 times when the nerve is being stimulated. There can be little doubt that a large part of this increase must be due to the actual passage of the impulses along the nerve from the seat of excitation.

[1] Thörner, "Ztschr. f. allg. Physiol.," viii. p. 530, 1908; x. p. 351, 1910.
[2] Waller, Croonian Lecture, "Proc. Roy. Soc.," p. 308, 1896.
[3] Waller, "Physiology the Servant of Medicine," London, 1910.
[4] Shiro Tashiro, "Amer. Journ. Physiol.," xxxii. p. 107, 1913.

At the same time it must be remembered that in these experiments the part of the nerve actually traversed by the current was in the respiration chamber, and stimulation lasted for ten minutes. The heating effect of the current cannot be negligible, and, as he himself states, the carbon-dioxide output of resting nerve is increased by rise of temperature. Again, the passage of the current may have caused some liberation of acid which would decompose carbonates with the liberation of carbon-dioxide. The results would certainly be more convincing if we could have a comparison of the output from nerves in one case stimulated and allowed to conduct the impulses from end to end, and in the other case stimulated but with a ligature near the point of stimulation to prevent the impulses from reaching the main body of the nerve. If a difference were found in these two cases the proof that the impulses actually led to an increased output of carbon-dioxide would be satisfactory. It must be remembered that an increased output of carbon-dioxide does not imply a simultaneous absorption of oxygen. We have always to consider the possibility that the carbon-dioxide may be due not to an immediately preceding combustion but to the decomposition of carbonates by acid produced as a consequence of the nervous impulse or of the stimulating current. The work of Fletcher and Hopkins on muscle shows that there are many pitfalls to be avoided before we can trace the exact origin of an increase in the output of carbon-dioxide.

However, the whole body of evidence is, I think, sufficient to justify the conclusion that nerve uses oxygen and gives off carbon-dioxide when it is conducting nervous impulses. This confirms the inference from Adrian's experiments, that the nervous impulse depends for its transmission on the supply of energy by the nerve along its course. If this view is correct we may be justified in supposing that by its very nature the nervous impulse is dependent for its intensity only on the conditions which it encounters during conduction and not on the intensity with which it is initiated. This at any rate seems to be the hypothesis which best accords with the experimental facts at present

known. New observations may at any moment lead us to revise our views, but in the meantime we do best if we leave this point and inquire into other possible sources of variation. The next aim before us will therefore be to learn how the nervous impulse is modified by the conditions which it meets in the course of conduction.

CHAPTER VI.

THE EFFECT OF INCOMPLETE RECOVERY AFTER PREVIOUS CONDUCTION.

THE REFRACTORY PERIOD.

WE have become familiar with two possible conditions of a nerve, one the normal in which a single impulse is conducted at a fixed intensity without loss, and the other, produced by artificial means, in which the impulse gets weaker and weaker the further it has travelled. The distinction between these two types of conduction is fundamental because in normal conduction the impulse depends for its intensity only on the state of the nerve at the moment, whereas in conduction with a decrement the impulse in a nerve under constant conditions may be small if it has travelled far under those conditions or large if it has only just encountered them.

In studying the modifications of the nervous impulse we shall constantly have to derive our knowledge from experiments made on nerve in which conduction with a decrement has been induced by artificial means. The use of this technique is forced upon us by the fact that it is the only means we have of measuring the nervous impulse. But it may seem to you that we shall be building up a structure of academic knowledge concerning the behaviour of the nervous impulse under conditions which it never can encounter in the normal nervous system. And you may remember that I expressly stated my intention to avoid the study of abnormal conditions on conduction.

I am anxious therefore that you should realise at this point that in all probability conduction with a decrement is a normal happening in certain parts of the nervous system. The evidence for this statement cannot be given in full now, because it involves

the use of experimental methods which must first be described in detail. But the general nature of the evidence is that in the junctional regions of the nervous system, particularly the junction between motor nerve and skeletal muscle, the nervous impulse has been shown to behave just as it does in a tract of nerve in which conduction with a decrement has been artificially induced. There are indications, too, that conduction at the synapse may present the same features. The study of conduction with a decrement is therefore just as essential to an understanding of the nervous system as that of conduction in the normal nerve trunk. Indeed it is my conviction that for a proper knowledge of conduction in the reflex arc it is about the decrement that we most need to learn, since this is probably the distinguishing feature of conduction at the synapse, and it is the synapse which confers on reflex arc conduction its special properties. But I must not anticipate your judgment upon the evidence which I have to lay before you.

The Alteration of Nerve by the Passage of a Nervous Impulse.

Up to this point we have dealt with the nervous impulse as an isolated disturbance passing down a nerve previously at rest. In the normal life of the nervous system this is by no means the most frequent case. The work of Piper,[1] Veszi,[2] Dittler and Günther[3] has established the fact that even the shortest activities of the motor side of the nervous system are groups of impulses following one another in quick succession. Only the first of these impulses travels along resting nerve. The rest are subject to what is perhaps the most important of all conditions modifying the conduction of the nervous impulse, the period of incomplete recovery after previous conduction. To this we must turn our attention.

That the activity of an excitable tissue might be followed by

[1] Piper, "Elecktrophysiol. menschl. Muskeln.," Berlin, p. 79, 1912.
[2] Veszi, "Ztschr. f. allg. Physiol.," xv. p. 245, 1913.
[3] Dittler and Günther, "Arch. f. d. ges. Physiol.," clv. p. 251, 1914.

a period of enforced rest is an observation which has long been recognised in the case of the heart muscle. A single stimulus acting on the resting muscle will produce a contraction, but two stimuli will not produce two contractions unless the interval between the stimuli exceeds a certain duration which is of the order of 0·5 sec. in the frog's ventricle. Thus for a certain period after an effective stimulus the muscle will not respond to a second stimulus; the tissue is in the "refractory" state and needs a certain time before it will have recovered sufficiently to respond again. In heart muscle the effect is very easily observed because the refractory period is of long duration and needs no elaborate timing apparatus for its measurement. The first evidence in support of a similar refractory phase in nerve was brought forward by Gotch and Burch[1] in 1899.

The electric response of the nerve was determined by a capillary electrometer and photographic records were made of the electric responses to two stimuli separated by extremely short time intervals. They found that if the interval between the stimuli was short enough only one electric response was produced, although there would have been no difficulty in detecting a second response if it had appeared. Gotch analysed these results in a later paper.[2] In a nerve cooled to 4° C. he found that the two stimuli had to be separated by an interval of ·007 sec. before a second electric response appeared; in the nerve at 12° C. the necessary interval was ·003 sec. Thus in regard to its electric response the nerve shows a refractory period comparable to that observed in the heart, but of much shorter duration. However, the production of the electric response in a nerve is not the only indication of its activity, indeed Gotch himself was inclined to the view that under certain conditions an impulse might pass down the nerve without giving rise to any measurable electric response. Consequently it became necessary to inquire if there was any other evidence of a refractory phase following a successful stimu-

[1] Gotch and Burch, "Journ. of Physiol.," xxiv. p. 410, 1899.
[2] Gotch, "Journ. of Physiol.," xl. p. 267, 1910.

lation of the nerve. This evidence was supplied by Boycott.[1] As an index of the success or failure of the stimulus he made use not of the electric response but of the contraction of the muscle in connection with the nerve. A single maximal stimulus applied to the nerve produces a twitch of constant strength in the muscle, and this is indicated as a contraction of constant height on the recording drum. Two stimuli separated by a sufficiently long time interval produce a summated contraction of greater height by the fusion of two twitches. However, when the interval between the stimuli is shorter than about ·0025 sec. (at 15° C.), the contraction is no greater than that due to the first stimulus alone. As the interval is increased gradually the contraction suddenly rises to a greater height and thereafter it continues to rise gradually as the stimuli are separated. The sudden rise is very sharply marked, and occurs within very small time limits; it is obviously a very different affair from the gradual rise which follows. The former indicates the first appearance of a second contraction in answer to the second stimulus, the latter is a mechanical effect due to the gradually increasing interval between the two contractions. It is clear then that a second stimulus occurring very soon after the passage of the nervous impulse is unable to set up a second twitch in the muscle, and this confirms the view that the tissue enters into a refractory phase after the impulse has passed down it.

At first sight these observations might be taken to prove that the refractory condition is due directly to the passage of the first nervous impulse. However, the nerve has been subjected not only to the passage of the first impulse, but also to the local chemical and electrical effects of the stimulus which sets this impulse in motion. It is at least conceivable that the refractory state is a direct consequence of the electric current which formed the first stimulus and is quite independent of the nervous impulse set in motion by this current. To test this point Gotch[2] tried the effect of sending in the two stimuli in different parts of the

[1] Boycott, "Journ. of Physiol.," xxiv. p. 144, 1899.
[2] Gotch, "Journ. of Physiol.," xl. p. 267, 1910.

nerve, so that the second stimulus should not fall on tissue which had been exposed to the local effects of the first. The refractory period was still obtained with this arrangement, and though Gotch considered that local "excitation fatigue" might have some influence when both stimuli fell on the same point, he concluded that the refractory state was due in part at least to the passage of the nervous impulse. The question was settled by further experiments on the same lines by Bramwell and Lucas.[1] They measured the refractory period by determining the interval between the two stimuli necessary to give a summated contraction in the muscle, and they compared the interval required (*a*) when the two stimuli were sent in at the same point on the nerve, and (*b*) when they were sent in at different points separated by a measured length of nerve. In the first case both stimuli were sent in at X (Fig. 6), and in the second case the

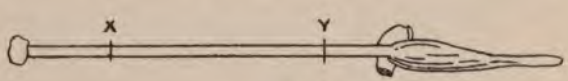

FIG. 6.

first stimulus was sent in at X and the second at Y. If the local effect of the stimulus at X has any influence on the length of the refractory period, we should expect to find the interval for muscular summation longer in case (*a*) where the stimuli were together than in case (*b*) where the second stimulus would be removed from the sphere of action of the first. Actually the interval in case (*a*) was always shorter than that in case (*b*), and the difference agreed within the limits of experimental error with the time which would be taken in the conduction of the nervous impulse from X to Y. This result can only mean that the refractory period is set up by the nervous impulse in its passage down the nerve. The period is longer in case (*b*) than in case (*a*), because the first impulse has to travel from X to Y before the tissue at Y is thrown into the refractory state, and for this reason the difference will be equal to the time taken in conduction from X to Y. Very intense and prolonged stimu-

[1] Bramwell and Keith Lucas, "Journ. of Physiol.," xlii. p. 495, 1911.

lation may cause some "excitation fatigue" in the region stimulated, and a current of moderate strength may cause a slight local depression of excitability,[1] but under ordinary conditions the refractory period must be due entirely to the passage of the first nervous impulse and not to the local after-effects of the first stimulating current.

We may conclude then that the passage of a nervous impulse brings about a condition in which the nerve is temporarily unable to respond to a second stimulus. This inability to respond might be due to two distinct factors. The nerve might be in such a state that a second stimulus was unable to effect the local change required for setting up a nervous impulse, or it might be unable to conduct an impulse even if this had been set up. In other words, the defect might be one either of excitability or of conductivity. As we shall see, the activity of the nerve is modified in both directions, and the phenomena of the refractory period are due to the impairment and recovery of excitability and also of conductivity. It is important to preserve a clear distinction of these two aspects of recovery. The recovery of local excitability is the easiest to investigate and most work has been done on this problem; but for an understanding of the processes of conduction under normal conditions it is more important to investigate the way in which conduction is impaired by the passage of a nervous impulse and the stages through which the conductivity of the nerve passes on its return to the normal.

The earliest work on the subject of the refractory period was concerned only to demonstrate that the passage of an impulse was followed by a period in which the nerve was inexcitable to the strongest stimuli. No attempt was made to trace the subsequent recovery of the tissue after the period of complete inexcitability was over. Trendelenburg[2] was the first to map out the course of this recovery by quantitative measurements. His experiments were made on the auricle and ventricle of

[1] Levinsohn, "Arch. f. d. ges. Physiol.," cxxxiii. p. 267, 1910.
[2] Trendelenburg, "Arch. f. d. ges. Physiol.," cxli. p. 378, 1911.

the frog, and they consisted in determining the strength of stimulus necessary to produce a contraction when the stimulus was timed so as to fall towards the end of the refractory phase due to a previous contraction. He found that during the earlier stages of the contraction the tissue is completely inexcitable, but towards the end the excitability begins to return. At first the excitability is very small, very strong stimuli being required to set up a second contraction, but there is a gradual return of excitability, and soon after the contraction has subsided the tissue responds to stimuli which are only just strong enough to affect the resting muscle. Thus in the heart the recovery takes place gradually, and there is a period in which the tissue will respond only to stimuli of greater strength than those which are effective in the resting muscle. This period of incomplete recovery is usually known as the relative refractory period to distinguish it from the absolute refractory period when the tissue is completely inexcitable.

Shortly after this Fröhlich published a curve[1] showing what he took to be the course of recovery in nerve. This curve was based on theoretical considerations, and in several respects it does not agree with the actual course of recovery as determined experimentally. In 1912 Adrian and Lucas[2] succeeded in mapping out the course of recovery in nerve by a method similar to that of Trendelenburg. A muscle-nerve preparation was excited by a maximal stimulus and the height of the contraction was recorded. A second stimulus was timed to fall very soon after the first, and the strength was adjusted until it was just sufficient to produce a summated contraction in the muscle. To avoid any local effects due to the first stimulating current it was arranged that the second should fall on another part of the nerve. As the interval between the two stimuli is increased there is first of all a period, corresponding to the absolute refractory period, during which the second stimulus has no effect however strong it may be. Then a very strong stimulus is able

[1] Fröhlich, "Ztschr. f. allg. Physiol.," ix. p. 86, 1909.
[2] Adrian and Keith Lucas, "Journ. of Physiol.," xliv. p. 68, 1912.

to set up a summated contraction, and with greater intervals the strength required becomes weaker and weaker until eventually a summated contraction is produced by a stimulus which would be only just strong enough to excite the resting nerve. Fig. 7 shows the recovery of excitability determined in this way in a frog's gastrocnemius-sciatic preparation at 14·8° C. The abscissæ give the time interval between the two stimuli, and the ordinates give the excitability measured in percentages of the normal excitability of resting nerve. These values are of course pro-

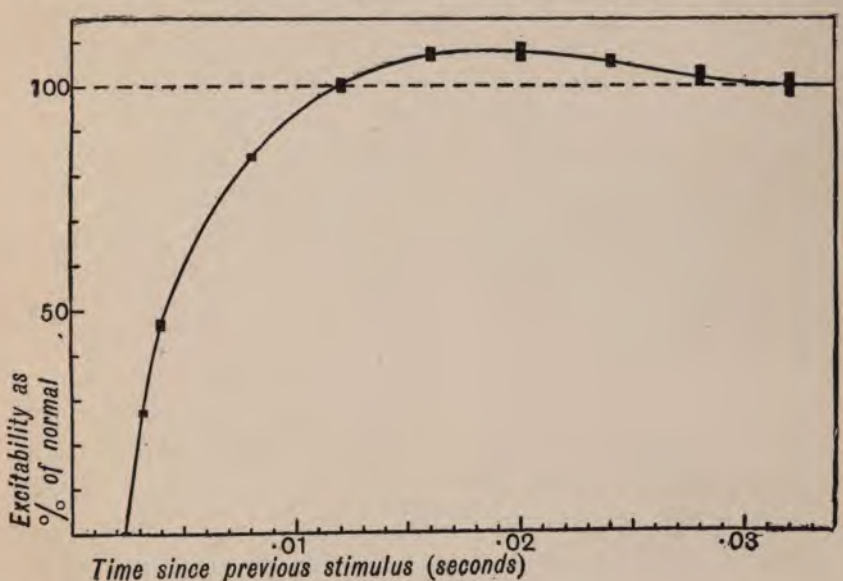

FIG. 7.

portional to the reciprocal of the current strength required to excite.

Since the original observations were made the curve has been determined on a large number of preparations with the same result. Complications are introduced when the nerve is not all at a uniform temperature, but these do not affect the result. Evidently the course of recovery may be divided into three distinct periods. There is first of all the absolute refractory period when the nerve is inexcitable. This is followed by the relative refractory period in which the excitability returns gradu-

ally to normal. However, the process of recovery does not end there, for the curve overshoots the mark and there is a third period during which the nerve is actually more excitable than it is in the resting state. For the present we must content ourselves with noting the existence of this period of increased excitability. Its detailed discussion will follow later.

So far, then, we have traced the course of recovery in terms of the strength of stimulus needed to excite the nerve. In a sense this bears some relation to the parallel question of the recovery of conductivity, because the success of the second stimulus demands not only a successful initiation of the nervous impulse but also a successful conduction. However, Adrian[1] has shown that the recovery curve determined as in Fig. 7 is certainly the expression of a purely local recovery of the mechanism of excitation. The time relations of the curve depend on the temperature of the nerve immediately under the stimulating electrodes, and are not affected by alterations in the temperature of other parts. Indeed, the evidence we have examined hitherto does not give us any ground for assuming that the power of conduction of the nerve is altered at all by the passage of the nervous impulse. The failure of an early second stimulus might be due entirely to a temporary breakdown in the mechanism of excitation, and there might be no hindrance to the conduction of an impulse following on the heels of a predecessor if only the second impulse could be started by setting it up in some region where the recovery was more advanced.

Consequently we have to inquire whether there is any impairment of conductivity in the nerve corresponding to the impairment of excitability which follows a previous impulse. We have to find whether there is any period in which the nerve is absolutely unable to conduct an impulse, and, if so, how the recovery of conductivity takes place. Finally, is the recovery followed by a period of enhanced conductivity corresponding to the period of enhanced excitability?

The first observations which have a bearing on the question

[1] Adrian, "Journ. of Physiol.," xlvi. p. 384, 1913.

are those of Boycott.[1] He found that the least interval at which two stimuli, applied to the nerve, would give a summated contraction in the muscle was increased by cooling a region of the nerve between the point stimulated and the muscle. This cooling would not affect the rate of recovery of excitability at the point stimulated, and therefore the least interval at which a second stimulus could set up a second nervous impulse would remain unchanged. If there is no impairment of conduction following the passage of the first impulse, there is no reason why cooling the nerve through which the impulses must pass should have any effect at all. The fact that it lengthens the interval for muscular summation can only mean that an early second impulse is unable to pass through the cooled region because it cannot be conducted through this region until the recovery is more advanced. Thus in the early stages of the refractory period the nerve is not only unable to be excited but also unable to conduct. The impairment in both these functions is well illustrated by mapping out the recovery curve (i.e. the curve relating the strength of the second stimulus to the interval at which it will give a summated contraction) in a preparation in which the nerve is cooled locally between the electrodes and the muscle. In Fig. 8[2] the dotted curve was obtained with the whole preparation at 16° C. It should be noted that in this figure the ordinates represent current strength directly and not their reciprocal excitability. The full curve was obtained after a short length of nerve between the seat of stimulation and the muscle was cooled to 3° C. In this case the curve is made up of two portions, one descending vertically at ·007 sec. and the other following the course of the dotted curve. An experimental analysis shows that the vertical part of the curve is an expression of the failure of conduction in the cooled region. An impulse set up earlier than ·007 sec. after the first will fail to reach the muscle because of the block to conduction in the cooled area, and the failure will be complete for all strengths of stimuli.

[1] Boycott, "Journ. of Physiol.," xxiv. p. 147, 1899.

[2] Adrian, "Journ. of Physiol.," xlvi. p. 391, 1913.

Once this interval is passed, the cooled area has recovered sufficiently to conduct an impulse again. Thereafter the impairment of local excitability comes into play and the strength of the stimulus is now the important factor since it determines whether an impulse is set up or not. The rate of recovery of excitability in the region stimulated is not altered by cooling the peripheral part of the nerve, and therefore the lower part of the curve agrees with that determined before the cooling.

These experiments show us that the passage of a nervous

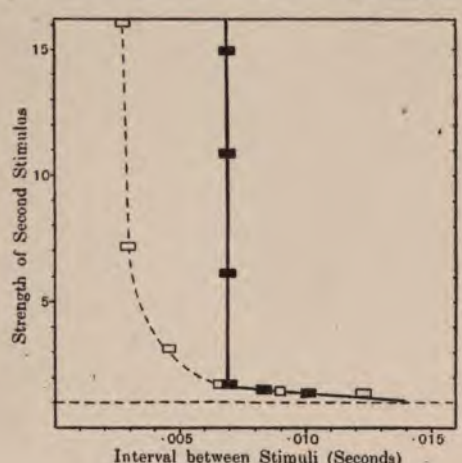

FIG. 8.

impulse is followed by a period during which the nerve is unable to conduct a second impulse, and they give us a means of measuring the length of this period. For instance, in the experiment quoted above, the cooled part of the nerve was unable to conduct an impulse following at less than ·007 sec. after the first. However, they do not show how the recovery of conductivity takes place, whether there is any stage in which the conduction is impaired but not absolutely abolished, and, if so, how this impairment shows itself.

As a first suggestion we might suppose that during the period of incomplete recovery the nerve would conduct with a decrement, the impulse becoming smaller and smaller as it

passed away from the seat of excitation. To test this point Adrian and Lucas[1] measured the least interval between two stimuli which would give a summated contraction when the stimuli were applied at different points along the course of the nerve. If a second impulse set up in the stage of incomplete recovery is conducted with a decrement, an impulse set up a long distance from the muscle would be less likely to reach it without extinction than an impulse set up in the same stage of recovery at a point nearer the muscle. Consequently the interval required for muscular summation should be prolonged by shifting the electrodes away from the muscle and so increasing the path down which the second impulse would have to travel. Actually it was found that the length of nerve included between the electrodes and the muscle made no difference at all to the interval necessary for the successful conduction of the second impulse. It is clear then that the stage of incomplete recovery, if it exists, is not associated with conduction with a decrement, and we must look for some other sign of impaired function.

We have seen that in its passage through a region of decrement the impulse became progressively less and less able to travel, and we have measured the intensity of the impulse in terms of its ability to face a region of decrement without extinction. In normal nerve in the resting condition we found that the intensity of the impulse was constant whatever the conditions under which it had started. Now it is conceivable that in the stage of incomplete recovery the nerve, although not conducting with a decrement, might be in such a state that it would be unable to conduct impulses of the normal intensity, but able to conduct impulses of an intensity less than normal. As recovery proceeded we might expect to find that the nerve would become able to conduct impulses of greater and greater intensity until finally its normal powers of conduction had completely returned. Evidently this suggestion may be tested by measuring the size of the second impulse in terms of the length it will travel in a region of decrement without extinction. If an impulse following

[1] Adrian and Keith Lucas, "Journ. of Physiol.," xliv. p. 96, 1912.

soon after a predecessor is less able to travel through a region of decrement than is an impulse set up in resting nerve, we may conclude that in the stage of incomplete recovery the nerve will only conduct impulses of less than the normal intensity. By relating the interval between the first and second impulse to the distance which the second impulse can travel in the region of

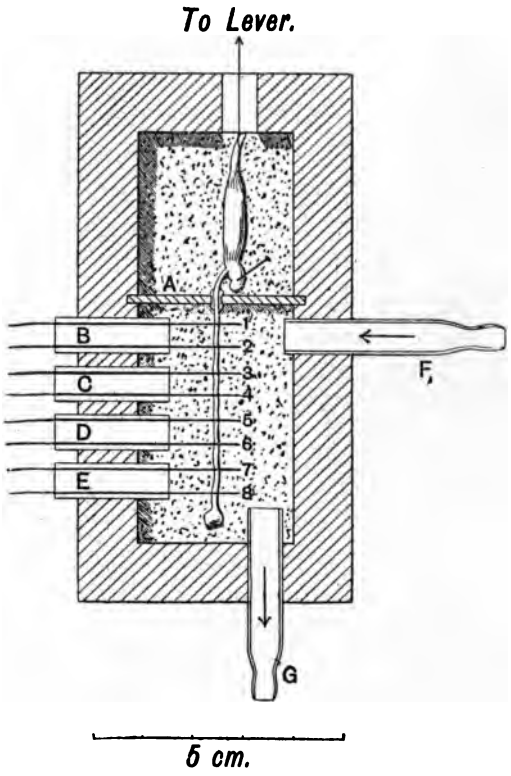

FIG. 9.

decrement, we shall be able to map out the course of returning conduction just as we mapped out the course of returning excitability.

An investigation on these lines was carried out by Adrian and Lucas.[1] A frog's sciatic was treated with alcohol vapour to bring about conduction with a decrement, and the summated con-

[1] Adrian and Keith Lucas, "Journ. of Physiol.," xliv. p. 93, 1912.

traction of the gastrocnemius was used to record the success or failure of the second impulse in passing through the affected region. Pairs of stimuli were sent in at six different points which were respectively 30, 24, 20, 15, 10, and 6 mm. from the distal end of the narcotising chamber, and the least interval required for a summated contraction was determined at each point at different stages of narcosis. Fig. 9 shows the arrangement of

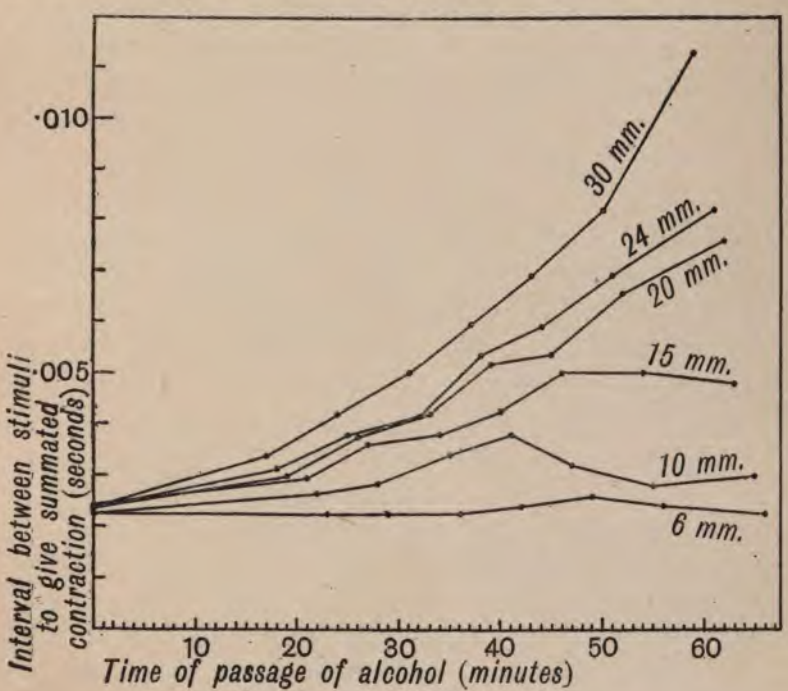

FIG. 10.

the muscle-nerve chamber, the alcohol vapour entering by the tube F and leaving by G. Fig. 10 shows a record of the intervals between the two stimuli necessary to give a summated contraction when the distances which the impulses would have to travel were 30, 24, 20, 15, 10, and 6 mm. As the narcosis deepens the interval starts to rise at the electrode furthest from the muscle and then at the other electrodes. At any given stage of narcosis the interval is always greater as the distance between the electrodes and the muscle is increased. Thus the interval at which

the second impulse must follow the first if it is to succeed in reaching the muscle varies with the distance it has to travel in the region of decrement; in other words, the intensity of the second impulse varies with the interval between it and the first. Fig. 11 is constructed from the results of Fig. 10, and shows the relation between the time at which the second impulse is set up

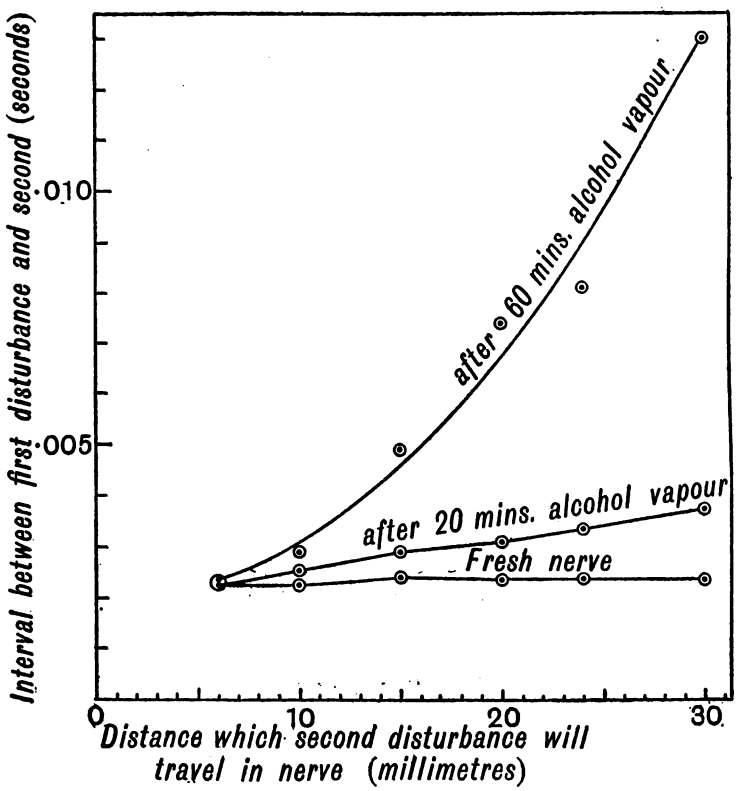

FIG. 11.

and the distance which it will travel without extinction. Curves are constructed for three different stages of narcosis. It will be seen that before the treatment with alcohol has begun ("fresh nerve") the time at which a second impulse can be set up and reach the muscle is independent of the distance which it has travelled, since the earliest second impulse which can be set up undergoes no appreciable reduction as it passes down the nerve.

After the alcohol has passed for 20 minutes the nerve begins to show a slight decrement, and this is much more pronounced after the alcohol has passed for an hour. At this time an impulse set up ·005 sec. after the first will travel only 15 mm. without extinction, whereas an impulse set up at ·013 sec. will travel for 30 mm. This can only mean that the intensity of the impulse set up ·005 sec. after the first is smaller than that set up at ·013 sec. Without attempting to push any further the quantitative inferences to be drawn from experiments of this type, we may safely infer that the earlier the second impulse is set up the less is its intensity, and that the relation between the time of recovery and the duration is a continuous one.

One possible objection must be dealt with; in these experiments the nerve was treated with alcohol and the stimuli were applied to the region so treated. The obvious effect of the alcohol was to increase the least interval at which two stimuli would give a summated contraction in the muscle. We have explained this by supposing that a second impulse set up at an early stage of recovery would be too small to face the decrement brought about by the alcohol. However, it is at least conceivable that the increased interval was due to a slowing of the recovery process in the narcotised area. The alcohol might have increased the time during which the nerve was inexcitable and unable to conduct at all, and this would naturally increase the least interval at which a summated contraction could be obtained. A consideration of Fig. 10 shows at once that this view cannot be maintained. The alcohol affects all parts of the nerve in the narcotising chamber, and therefore if it slows the recovery process at the electrode furthest from the muscle, it must slow it equally at the other electrodes. However, even in the deepest stages of narcosis when the interval for muscular summation had risen to ·01 sec. at the furthest electrode, it was still unchanged at the electrode 6 mm. from the distal end of the chamber and only raised from ·002 to ·003 sec. at the electrode 10 mm. away. Consequently if any slowing of recovery does take place it must be of very slight extent, and its effect on

the interval for muscular summation must be quite negligible in comparison with the effect of the decrement in extinguishing the small impulses set up in the early stages of recovery. Indeed later experiments[1] have shown that alcohol has no effect at all on the rate of recovery of nerve, and that the whole effect is due to the decrement in conduction.

The exact course of the recovery of conductivity has yet to be mapped out, though there is evidence that it follows closely the course of the recovery of excitability. The evidence which points to a period of enhanced conductivity following the period of depression is described in the next section. The results of this section may be summed up as follows:—

We have seen that the passage of a nervous impulse leaves in its wake a period of depressed function known as the refractory phase. In the earlier stages the nerve is inexcitable to any stimuli and also quite unable to conduct impulses which have been set up in some region where the recovery was more advanced. The excitability of the nerve returns gradually during the relative refractory period and the power of conduction also returns gradually. The impairment in conduction is of a different kind from that brought about by a narcotic. The nerve does not conduct with a decrement, but it will not conduct impulses of the normal intensity. The intensity remains constant as the impulse travels down the nerve, but it is less than the normal because the impulse can be extinguished by compelling it to undergo a decrement which is not great enough to extinguish an impulse of the normal intensity. The intensity of the second impulse becomes gradually greater and greater as the interval between it and the first is increased.

The evidence has been discussed at some length because the phenomena of the refractory phase are of fundamental importance in any attempt to explain the normal working of the nervous system. However, the account is not yet complete, and we must pass on to consider the phase of exaltation which follows phase of incomplete recovery.

[1] Keith Lucas, "Journ. of Physiol.," xlvi. p. 470, 1913.

CHAPTER VII.

THE SUPERNORMAL PHASE.

WHEN determining the course of recovering excitability in a nerve recently traversed by a nervous impulse, Adrian and I did not confine our attention to the so-called relative refractory period in which the excitability is less than normal. We carried our observations past the moment at which the excitability had regained its normal level, and found a period in which the nerve is actually more excitable than when at rest. It should be recalled that in these experiments the second stimulus fell on a point traversed by the first nervous impulse, but not subjected directly to the first stimulus. This fact is important because, as Gildermeister[1] and Levinsohn[2] have shown, a part of an excitable tissue actually traversed by a short current may show a subsequent depression of excitability which is the direct local consequence of the current and not of the passage of an impulse. If the precaution of stimulating at different points with the two stimuli is not observed, this local effect may mask the supernormal phase of excitability which Adrian and I found.

We were in doubt at first whether the supernormal phase showed a genuine heightened excitability of the tissue, or might perhaps be due to an increased electric conductivity making the stimulus abnormally strong. The effect, however, persists when an external resistance of 100,000 ohms is included in the exciting circuit. We were also able to show that any increase of electric conductivity which the recovering nerve may exhibit is too small to account for the phenomenon. This we did by including in the exciting circuit of the coil which delivered the

[1] Gildermeister, "Arch. f. d. ges. Physiol.," cxxiv. p. 447, 1908; "Festschr. f. L. Hermann," p. 53, 1908.

[2] Levinsohn, "Arch. f. d. ges. Physiol.," cxxxiii. p. 267, 1910.

second stimulus a second nerve which was not excited by the first stimulus. This second nerve did not show any increase in excitability, though of course there was included in the circuit by which it was excited a stretch of the first nerve, whose conductivity might be supposed to be increased during recovery. The arrangement of this experiment is shown in Fig. 12. The nerve x is stimulated with one stimulus at a^1. The second stimulus affects this nerve at b^1 and the nerve y at c^1. Though the point b^1 is abnormally excitable after the nervous impulse has passed it, the point c^1 requires the same current as it does if x has not been stimulated. If there were a sufficiently large increase of electric conductivity in the tract bb^1 to account for the

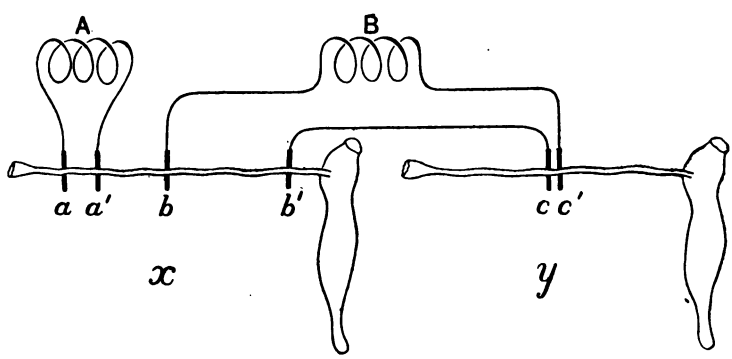

FIG. 12.

apparent supernormal excitability at b^1, then the strength of the current passing through bb^1 and cc^1 would be sufficiently increased to produce a noticeable alteration when c^1 was stimulated.

By such methods we were led to conclude that the supernormal phase did represent a real increase of excitability in the nerve. Since that time I have explored the supernormal phase in a nerve leading to the adductor muscle of the claw of the crayfish.[1] Here I find the supernormal phase more strongly marked than it is in the sciatic nerve of the frog. In the sciatic nerve the excitability at the maximum of the supernormal phase rose only to 108 per cent of the normal in the most favourable cases. In the crayfish nerve I have found it as high as 139 per cent

[1] Keith Lucas, "Journ. of Physiol.," li. p. 1, 1917.

of the normal; in other words, the current required to excite was only 72 per cent of that required in the resting nerve. Fig. 13 shows a case observed in the crayfish. The values plotted here are strengths of current required to excite, and in this experiment the lowest current strength was 80 per cent of the normal, or the excitability rose to 125 per cent.

The idea that the refractory phase may be followed by a supernormal phase is by no means new. The electric response

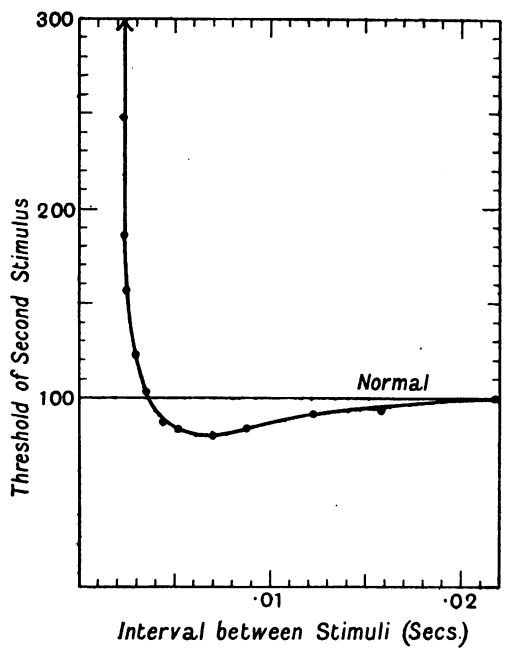

FIG. 13.

of a nerve or muscle is increased by previous activity, as Waller,[1] Garten,[2] Wedensky,[3] Samojloff,[4] and Beritoff[5] have shown. Wedensky has named the period of increased electric response "phase exaltée" as the counterpart to the "phase refractaire," and Beritoff speaks of the phenomenon as an "increase of excit-

[1] Waller, Croonian Lecture, "Phil. Trans.," 1896.
[2] Garten, "Beiträge z. Physiol. der Marklosen Nerven," Jena, p. 83, 1903.
[3] Wedensky, "Trav. d. labor. d. Physiol.," St. Petersburg, iii. p. 134, 1908.
[4] Samojloff, "Arch. f. (Anat. u.) Physiol. Suppl.," p. 1, 1908.
[5] Beritoff, "Ztschr. f. Biol.," lxii. p. 125, 1913.

ability" ("Zunahme der Erregbarkeit"), though showing clearly that he refers to an increase in the amplitude of the electric response. It is important, however, to distinguish these phenomena clearly from the period of supernormal excitability which Adrian and I have described. A loose application of the word *excitability* or *Erregbarkeit* leads to unnecessary confusion in a subject already difficult enough. If the electric response is observed to be increased, it is almost as easy to call the effect an increase of the electric response as to call it an increase of excitability, and the former is certainly a much better description of what is observed. A closer analysis of this phenomenon must be left to the next section. For the present it may be taken as evidence of a period of enhanced function following recovery, but it is not very clear what particular function we are dealing with. On the other hand, the case which Adrian and I observed, in which the nerve after conducting one impulse can be excited by a weaker current than before, does give fairly conclusive evidence of an increase of the local excitability of the nerve. It is true that a nerve made up of fibres of varying excitability might show an effect of much the same kind owing to an increase in conductivity in the later stages of recovery. We should have to suppose that those fibres in which the weakest current would set up an impulse were for some reason unable to conduct an impulse successfully to the muscle unless the conductivity of the nerve was increased above its normal value. In the resting nerve a stimulus only just strong enough to excite these fibres would have no effect on the muscle because the impulses set up in them could not be conducted successfully. If the conductivity of the fibres was increased after recovery from the refractory state, the stimulus which was formerly ineffective would now be able to produce an effect in the muscle. This would give the illusion of an increased excitability, though in reality it would be due to an increased conductivity in the fibres which were formerly unable to affect the muscle. As we shall see, there is some evidence that even in a fresh preparation some of the nerve fibres may be unable to conduct a single impulse to the muscle,

but it is certainly unlikely that these fibres should always turn out to have a greater excitability than any of the others in the nerve. This possibility is a good illustration of the difficulties which are encountered in dealing with a nerve made up of many fibres which do not all behave in precisely the same way. However, the best argument in favour of the observed effect being due to an increased local excitability lies in the fact that the recovery curve is continuous throughout. It shows no signs of being made up of two curves, one comprising the period of recovery from zero to normal and the other the supernormal period. We have seen that the earlier part of the curve is a true expression of the recovery of local excitability and is not concerned with conductivity, and therefore we have strong grounds for assuming that the same function is involved in the later part of the curve where the strength of stimulus is less than the normal.

We may take it then that the phase of impaired excitability is followed by one in which the excitability is greater than normal, and I will go on to consider the evidence that there is also a phase of recovery in which the nervous impulse is conducted better than it is in resting nerve.

The proof comes as usual from experiments on the passage of a nervous impulse through regions of decrement. Goldscheider[1] narcotised a nerve with alcohol and found a stage at which a single stimulus did not succeed in causing a contraction of the muscle, whereas the same stimulus was successful if repeated. Fröhlich[2] showed the same effect with ether. Adrian and I[3] found that if nerve or muscle were raised locally to 42° C. the region so heated failed to conduct a single impulse, but conducted a succession of impulses following one another closely. These observations show in general that there is a phase of recovery at which the nervous impulse gets further through a region of decrement without extinction than it does when the nerve is at rest. We attempted to get some idea of the time

[1] Goldscheider, "Ztschr. f. Klin. Med.," xix. p. 180, 1891.
[2] Fröhlich, "Ztschr. f. allg. Physiol.," iii. p. 473, 1904.
[3] Adrian and Keith Lucas, "Journ. of Physiol.," xliv. p. 80, 1912.

after a previous impulse at which this improved conduction was to be found. We adopted the usual method of making an artificial region of decrement in a motor nerve with alcohol. We waited until the decrement had become so intense that a single stimulus just failed to pass through it and affect the muscle. When this stage was reached we sent down two impulses at a definite time interval and determined whether the second succeeded in passing the region of decrement and affecting the muscle. We found that if the second impulse followed at an interval of ·016 sec. it also failed; if it followed an any interval between ·024 sec. and ·075 sec. it passed the decrement successfully; at an interval of 0·1 sec. it failed again. Under favourable conditions the better conduction of the second impulse could be observed even when the narcosis was considerably too deep to allow the passage of a single impulse. These experiments must not be taken as defining accurately the duration of the period of supernormal conduction. It is difficult to maintain an artificial decrement in a steady state, and consequently the number of observations which can be made on one preparation is small. However, this much is clear, that to the phase of impaired conduction, which we have already recognised, there succeeds a phase of supernormal conduction before normality is finally reached. The time relations of these phenomena in frog's sciatic nerve at 15° C. can be roughly set out as follows:—

Conduction is impossible from 0 to ·003 sec. after a previous impulse.

„ „ impaired „ ·003 to ·015 sec. „ „

„ supernormal „ ·015 to 0·1 sec. „ „

A knowledge of these facts opens to us a whole range of possibilities in the regulation of nervous activity. According as we time impulses in the nervous system to follow one another at a shorter or a longer interval, we can make them less or more capable of being conducted through any regions of decrement which the system may contain. If there is a region of decrement such that a normal impulse just cannot pass, then impulses of

moderate frequency may pass it successfully, while impulses of a high frequency may not only fail to pass it, but may by their frequency prevent any other impulses finding their way through. Let us turn now to consider how these possibilities work out in practice.

CHAPTER VIII.

SUMMATION IN CENTRAL AND PERIPHERAL TISSUES.

THE work of Setschenow[1] first called attention to the important part played by "Summation" in the activity of the reflex arc. He showed that a frog with cerebrum removed gave no reflex response to a single induction shock applied to a sensory nerve, but would respond if a like stimulus was repeated frequently, for example, twenty-six times a minute. Stirling[2] investigated the phenomenon systematically, and found that the interval between the beginning of stimulation and the reflex response bore a relation both to the strength and to the frequency of the stimulus. Within certain limits the stronger the stimulus was, and the more frequent its repetition, the less was the interval. Moreover, the greater effectiveness of frequent stimulation was made clear by the fact that in most cases the greater the frequency of stimulation the less was the total number of stimuli necessary. He found also that single stimuli would call forth no reflex response unless made so strong that their effect was in reality a repeated excitation. The failure of even very strong stimuli to produce a reflex response, though they were in all probability strong enough to send an impulse along the afferent nerve, suggests that this summation in the reflex arc depends on the failure of the first nervous impulse to pass through the centre and the success of a subsequent impulse.

The recent work of Lapicque,[3] in which the central end of the cut sciatic nerve on one side was stimulated and the reflex

[1] Setschenow, "Physiol. Studien," u.s.w., Berlin, 1863; "Ann. d. Sci. Natur," xix. p. 109, 1863; "Ztschr. f. rat. Med.," xxiii. Nr. 6, 1864 (and xxiv. p. 292, 1865); "Ueber die elekt. und chem. Reizung," u.s.w., Graz, 1868.

[2] Stirling, "Arbeiten aus d. Physiol. Anstalt zu Leipzig," p. 223, Leipzig, 1875.

[3] Lapicque, "C. R. Soc. de Biol.," lxxii. p. 871, 1912.

contraction of the other foot was observed, confirms Stirling's observation that the strength of stimulus required to produce a reflex response becomes less as the frequency is increased within certain limits. Lapicque finds that for the reflex response of the frog to stimulation of the skin the strength of current becomes constant when the frequency has reached a value between ten and twenty a second. The important feature of his observation is that the frequency of stimulation at which the strength of stimuli required reaches a minimum changes with the temperature of the cord but is independent of the temperature of the seat of excitation. This fact demonstrates the truth of the inference already drawn from Stirling's work, that the greater frequency of stimulation determines not whether nervous impulses are or are not set up in the afferent nerve, but whether the impulses set up there succeed or fail in passing through the centre.

This summation of impulses at the centre is a process which often involves a large number of impulses before it succeeds. Stirling studied under different conditions how many stimuli were required before the reflex response was produced. In his experiments the number was frequently as high as fifty, and he records one case in which the response appeared only after 112 stimuli.[1] Sherrington,[2] too, speaks of cases in which the scratch-reflex in the dog did not appear until after the fortieth shock had been delivered. Between these extreme cases, however, and those in which the second stimulus succeeds in provoking the reflex there are all grades to be found even in the same preparation under varying conditions. The mere number of stimuli required to sum is therefore no logical ground for separating these phenomena in the reflex arc from certain simpler cases which have been observed in peripheral neuro-muscular mechanisms. I shall try to show you that there is an essential agreement between central summation and the phenomena seen by Richet in the peripheral system of the crayfish claw, or by Locke, Hoffmann, Adrian, and myself in the nerve-muscle preparation of the frog.

[1] Stirling, loc. cit. p. 252.

[2] Sherrington, "Integrative Action of the Nervous System," p. 37, London, 1906.

At the same time we have to recognise that all these cases are in a class entirely apart from the majority of observations on what is commonly called the summation of stimuli; the mechanism of the latter is fundamentally different and does not involve questions of conduction at all.

This distinction will be most clearly understood if we follow out briefly the history of our knowledge about the summation of stimuli. Engelmann[1] showed that in the ureter electric stimuli which failed to produce any contraction when acting singly would be successful when repeated at an interval of less than half a second. Romanes[2] made a like observation on the umbrella of one of the Medusæ, and Richet[3] in the same year gave an account of an apparently similar phenomena observed when stimuli are applied to the motor nerve of the claw muscles of the crayfish. A few years later Basch[4] showed the summation of stimuli in the frog's heart.

These observations formed the starting-point of knowledge on the subject. They were followed by numerous others which need not be considered in detail here.[5] There are, however, a few cases which will enter specially into the argument, and those I will mention now.

Weiss[6] studied the summation produced by short currents sent into a frog's motor nerve. Locke[7] placed a nerve-muscle preparation in 0·6 per cent sodium chloride, and found that after some time stimuli applied to the nerve were ineffective if single but caused contraction if repeated. The same phenomena were seen by Hofmann[8] after mild doses of curare, and by myself[9] after prolonged fatigue of the preparation.

In 1910[10] I attempted to give an explanation of some of these

[1] Engelmann, "Arch. f. d. ges. Physiol.," iii. p. 280, 1870.
[2] Romanes, "Phil. Trans. Roy. Soc.," clxvii. p. 659, 1877.
[3] Richet, "Travaux du laboratoire de M. Marey," p. 97, 1877.
[4] Basch, "Arch. f. (Anat. u.) Physiol.," p. 283, 1880.
[5] See Steinach, "Arch. f. d. ges. Physiol.," cxxv. pp. 239 and 290, 1908.
[6] Weiss, "Arch. Ital. de Biol.," xxxv. p. 413, 1901.
[7] Locke, "Centralb. f. Physiol.," viii. p. 167, 1894.
[8] Hofmann, "Arch. f. d. ges. Physiol.," xcv. p. 513, 1903.
[9] Keith Lucas, "Journ. of Physiol.," xliii. p. 76, 1911.
[10] *Ibid.*, xxxix. p. 461, 1910.

cases. I studied in frog's skeletal muscle, motor nerve, and ventricular muscle the time interval at which two short electric stimuli would sum and produce a visible effect when they were each 5 per cent below the strength required if they acted singly. I found the interval had to be shorter in nerve than in skeletal muscle, and shorter in skeletal muscle than in the heart.

From previous experiments there was ground for believing that in these tissues the local change produced at the electrodes by the stimulus tended to subside at different rates, namely, most rapidly in nerve, less rapidly in skeletal muscle, and less rapidly again in the heart. Accordingly I suggested that the action of the first stimulus was to produce a local change under the electrodes too weak to discharge a nervous impulse or wave of excitation, and that the second stimulus was effective if it fell on the tissue before this local change had subsided, because it could then add its local change to that still persisting, and so bring the whole up to the value required to discharge a propagated change.

Lapicque[1] was studying the problem at the same time, and found that such summation could be obtained only if the currents used as stimuli were of such short duration that they had no time to bring about the full local change of which they were capable if lasting longer. This fact agrees well with the explanation which I have offered, for if a current already lasts sufficiently long to produce all the local change of which it is capable, it will produce no greater local change when repeated.

Hill[2] then showed that on Nernst's hypothesis, that the local change induced in a tissue by an exciting current is a concentration of ions, such a type of summation could be calculated; there would be a necessary relation such as I have suggested between the interval necessary for summation and the rate of diffusion of the ions concerned.

Now if this does really represent the mechanism of this summation of subliminal stimuli, it follows that no summation

[1] Lapicque, "C. R. Acad. des Sci.," cl. p. 796, 1910.
[2] Hill, "Journ. of Physiol.," xl. p. 219, 1910.

will be observed unless the exciting action of the two stimuli concerned takes place at the same point on the tissue, for the changes supposed to sum are localised at the seat of excitation. Adrian and I [1] made experiments on this question in the sciatic nerve of the frog and found this inference verified. If the two stimuli fell on points 10 to 15 mm. apart along the nerve no summation could be observed. There exists then apparently this type of summation which is entirely a local matter, depending on the addition of two incomplete excitatory disturbances at the seat of excitation, and leading to the discharge of a propagated disturbance only when the two local effects have summed to an adequate value. It soon became clear, however, that not all cases of peripheral summation conformed to this type.

I have referred to the observation that if a nerve-muscle preparation is fatigued by long tetanisation of the nerve, or treated with mild curare or sodium chloride solution, a condition is reached in which a stimulus applied to the nerve produces no contraction of the muscle unless it is repeated at a short interval of time. Adrian and I [2] investigated a case of this kind, and found that the summation of the effects of successive stimuli took place equally well if alternate stimuli fell on different points of the nerve. In this case then it is clear that summation cannot have been due to the addition of local changes at the seat of excitation, but must have involved the sending out by the first stimulus of a nervous impulse which somehow failed to cause a muscular contraction, though it enabled a subsequent nervous impulse to do so. A significant fact about these cases was that they all involved the presence of some condition which if carried a little further was known to suspend completely the conduction from nerve to muscle. This is the result of more prolonged tetanisation of the nerve, of stronger curare, and of a longer stay in 0·6 per cent sodium chloride free from calcium. We were led therefore to imagine that the first stimulus sets up a nervous impulse which travels down the nerve and fails to pass from nerve to

[1] Adrian and Keith Lucas, "Journ. of Physiol.," xliv. p. 70, 1912.
[2] *Ibid.*, p. 75, 1912. Fig. 2.

muscle, but facilitates the passage of the junction by a second nervous impulse arriving a little later.

Almost at the same time Lapicque,[1] who had formerly expressed the view that summation in the central nervous system was, like summation in muscle, dependent on a residue of polarisation, published a paper[2] in which he pointed out that there were cases of summation which such an explanation could not cover. He drew attention to the important point that Richet in his work on summation in the crayfish, worked with alternately make and break induced shocks, and these, since they are alternating in direction, could not produce a local summation; they must have excited at different points on the nerve. Evidently then this was another example of the summation which involves two nervous impulses. I have since verified experimentally[3] this inference of Lapicque's, and find that Richet's summation behaves in just the same way as the summation which Adrian and I studied in the nerve-muscle preparation of the frog; it can be obtained with equal ease whether the two stimuli concerned fall on the same or on different points on the nerve. In the crayfish, as Richet originally pointed out, the condition in which one stimulus fails but two succeed is only obtained after the nerve has been stimulated a number of times and the contraction of the adductor muscle in response to a single stimulus has decreased and finally disappeared. There is then a close analogy between this phenomenon and the cases to which I have referred in which the condition is reached by a procedure which, if carried further, would suspend completely the conduction from nerve to muscle.

It is possible, however, even without such brutal treatment of the myoneural junction, to obtain evidence of this type of summation in the nerve-muscle preparation of the frog when it has been merely excised and placed in Ringer's solution. Samojloff[4] first noticed that when such a preparation is excited from the nerve the electric response of the muscle to a second stimulus is

[1] Lapicque, "C. R. Soc. de Biol.," lxiii. p. 787, 1907.
[2] Lapicque, "Livre Jubilaire Ch. Richet," 1912.
[3] Keith Lucas, "Journ. of Physiol.," li. p. 1, 1917.
[4] Samojloff, "Arch. f. (Anat. u.) Physiol.," Suppl. p. 1, 1908.

greater than that to the first, provided that the second stimulus follows the first within a certain range of time intervals. Adrian and I [1] found that the effect was absent if the stimuli fell directly on the muscle. Fig. 14 shows a comparison of the electric responses to second stimuli variously timed. The full curve, obtained by stimulating the muscle, shows that the second electric response gradually approaches but never exceeds the height of the first; the dotted curve, obtained by stimulating the nerve,

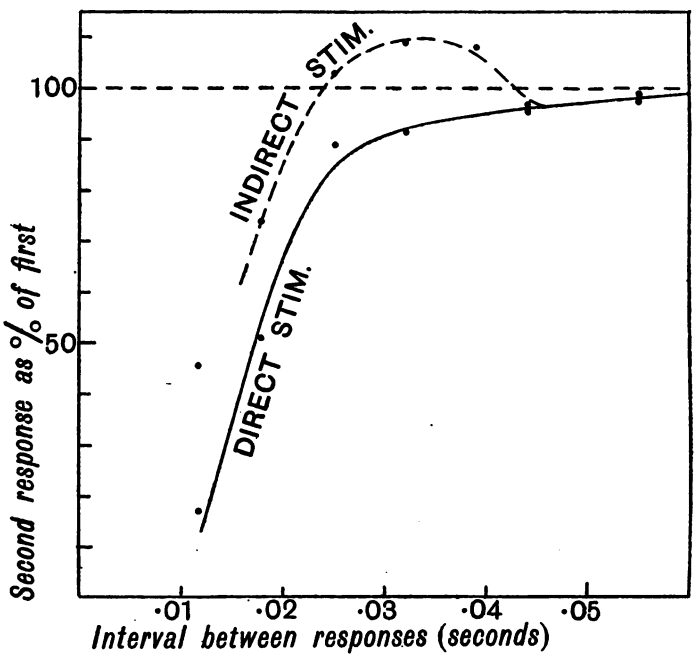

FIG. 14.

shows that over a certain range of time intervals, the response produced by a second stimulus does exceed that produced by the first. This experiment convinced us that the supernormal response to a second stimulus was not a property of the muscle. We then [2] tried to discover whether the effect depended on the seat of excitation of the second stimulus being rendered more excitable by the passage of the first nervous impulse. We found

[1] Adrian and Keith Lucas, "Journ. of Physiol.," xliv. p. 89, 1912.
[2] Loc. cit. p. 110.

that the time relations of the effect were not altered by cooling or warming the seat of the second stimulus. Fig. 15 shows the heights of second electric responses obtained in such an experiment. Whether the seat of excitation is at 7° C. (triangles) or at 23° C. (circles) the effect remains the same. Clearly then the increase of the second electric response must be due to better conduction

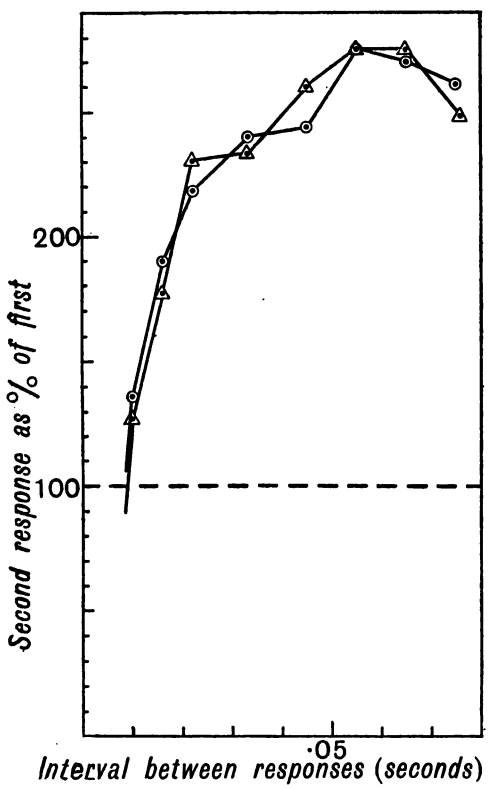

FIG. 15.

of the second impulse. Some nerve fibres probably fail to conduct a single impulse from nerve to muscle, but do conduct a second impulse suitably timed, and this takes place even in an apparently fresh preparation. Adrian and I found some preparations in which the effect was altogether absent at first, but appeared after such treatment as might be expected to render conduction from nerve to muscle less perfect.

CHAPTER IX.

ATTEMPTS TO EXPLAIN SUMMATION.

THE outcome of the experiments which I have described is to show that there is a type of summation obtainable in peripheral tissues which differs from the summation of incomplete local changes under the exciting electrodes in that the first stimulus does set up a nervous impulse which then fails to make the muscle contract. We have seen that this type of summation is always associated with a condition of imperfect conduction at the myoneural junction. There is an obvious analogy between this summation and the summation in the reflex arc studied by Stirling and by Lapicque. For in the latter case too there was evidence that the stimulus which produced no reflex response did set up an impulse in the afferent nerve, which was blocked in its passage through the centre. We have next to inquire whether our knowledge of the elementary phenomena of conduction can suggest any mechanism by which a first nervous impulse which failed in conduction might facilitate the passage of a nervous impulse which followed it.

Fröhlich[1] has suggested an explanation of the phenomena of summation seen in the central nervous system. He points out that, as he and Boruttau[2] found, the electric response of nerve when slightly fatigued may show a much prolonged descending phase. This prolongation he considers as an "excitation-remainder" to which subsequent waves of excitation can add themselves. The essential process of summation is therefore a prolongation of the conducted disturbance by what is really an initial fatigue, and the consequent possibility of summation in

[1] Fröhlich, "Ztschr. f. allg. Physiol.," ix. p. 71, 1909.

[2] Boruttau and Fröhlich, "Arch. f. d. ges. Physiol.," cv. p. 444, 1904.

the literal sense of adding. Verworn [1] has expressed this conception more in detail, and published diagrams showing how successive waves of excitation may be added one to another.

From these it is evident that the duration of a wave of excitation is supposed to be equal to that of the depressed excitability, which is usually called the relative refractory period, and that a second wave of excitation, occurring before the relative refractory phase due to its predecessor has passed away, is added to the remainder of the first excitation and so produces a stronger effect.

The fundamental assumption here made is that one nervous impulse can be added to another so as to produce a larger and more effective total. It is on this question that the experimental evidence must first be examined. The observations to which Fröhlich points in support of his statement are records of the electric response in narcotised nerve made by himself and Boruttau.[2] Gotch [3] has formerly shown from analysed records of the capillary electrometer that "there is no evidence of a second electrical effect of the excitatory type being able to summate with, and thus augment the E.M.F. of a state previously evoked by a maximal stimulus".

This result was obtained in nerve not subjected to fatigue or narcosis. Boruttau and Fröhlich found that when the nerve was affected by carbon-dioxide, the descending limb of the electric response was much drawn out so as to form a prolonged after-effect. Under these conditions successive responses, as seen in the uncorrected capillary electrometer records, mounted each from the after-effect of the preceding one and brought the mercury to a much higher level than it ever reached in the strongest single response.

These results naturally recall Waller's observations on the negative variation of nerve in carbon-dioxide. In spite of the fact that the capillary electrometer curves are not analysed (and

[1] Verworn, "Irritability," p. 208, New Haven, 1913.
[2] Boruttau and Fröhlich, "Arch. f. d. ges. Physiol.," cv. p. 461, 1904.
[3] Gotch, "Journ. of Physiol.," xxviii. p. 32, 1902.

the easy misinterpretation of such curves is well known to anyone who had worked with the instrument), we may admit that in fatigued or narcotised nerve the total electric response does become greater by the addition of each separate response to the remainder of its predecessor.

In these experiments the leads to the galvanometer are placed one on the part of nerve exposed to the carbon-dioxide, and the other on the injured end of the nerve. There is initially an E.M.F. between these points due to the injury. The precise observation made is that after each impulse has travelled down the part of nerve exposed to carbon-dioxide that part remains in a state more nearly like that of the injured end of the nerve. The fact is then that the "summation" of nervous impulses is inferred from the superposition of each electric response on a growing remainder of previous electric responses. We come then to the point that really concerns our inquiry. Are there grounds for believing that a nervous impulse is better conducted when the electric response which accompanies it is superposed on the remainder of a previous electric change? Of course if we identify the nervous impulse with the total electric disturbance, then we may say that the impulse is more intense when its own electric disturbance is added to a remaining previous disturbance. This is in effect what Fröhlich does when he uses the following words:[1] "The second factor which favours summation is the slow course of the waves of excitation. Thereby successive excitations find a strong excitation-remainder from their predecessors, to which they can sum themselves." This is merely a statement of the experimental observation in so far as the German word "Erregung," which I have translated by "Excitation," means electric response.

The statement serves as an explanation of summation only in so far as the addition of one "Erregung" to the remainder of another produces an "Erregung" which is more effectively conducted, and in this sense "Erregung" means the nervous impulse. Apparently the German word is used in both senses.

[1] Fröhlich, "Ztschr. f. allg. Physiol.," ix. p. 71, 1909.

This procedure does not really help us to understand summation, because it cannot extend our actual knowledge beyond the experimental observations about the electric response. All that we learn about the nervous impulse in this way is learned only about the electric response; any practical application of that knowledge will tell us only about the size of the electric response and not whether the nervous impulse is better conducted. And if we do not identify the electric response with the nervous impulse the presence of a remainder of electric response has not been shown to favour the conduction of a second nervous impulse. Such experimental knowledge as we have points rather in the opposite direction. The work of Gotch and Burch,[1] Boruttau,[2] Boruttau and Fröhlich,[3] and Tait[4] all shows that a prolonged electric response is associated with a prolonged refractory phase, and I am not aware of any experimental fact which gives evidence that during a persistent remainder of electric response a nervous impulse has any advantage which might outweigh the prolonged refractory condition.

This is in fact the point on which, as I believe, the hypothesis of Fröhlich and Verworn is insufficient. The whole problem of summation is how a previous nervous impulse, which we know to leave behind it a condition of impaired conduction (refractory phase), can favour the conduction of a following impulse. Their hypothesis gets over this difficulty by supposing that the impaired conduction can be outweighed by a simultaneous after-effect of the first impulse which acts in the opposite way, making the second impulse so large that it overcomes the state of impaired conduction. And the evidence for this antagonistic after-effect seems inadequate.

But surely in view of what we have learned of the elementary phenomena of conduction there is no need to postulate antagonistic effect proceeding simultaneously with the refractory phase and balanced against it. We have seen in studying the return

[1] Gotch and Burch, "Journ. of Physiol.," xxiv. p. 421, 1899.
[2] Boruttau, "Arch. f. d. ges. Physiol.," lxxxiv. p. 413, 1901.
[3] Boruttau and Fröhlich, "Arch. f. d. ges. Physiol.," cv. p. 444, 1904.
[4] Tait, "Quart. Journ. Exp. Physiol.," iii. p. 221, 1910.

of excitability after the passage of a nervous impulse that to the phase of diminished excitability, the relative refractory period, there succeeds a phase of supernormal excitability, and we have seen that the ability of a nerve to conduct an impulse passes through analogous phases of recovery; there is a phase in which conduction is less and less impaired, and then a phase in which conduction is better than in the resting nerve.

It seems possible that we may account for the improved conduction of a second impulse, which constitutes summation, by supposing that it rests on the existence of a favouring factor not simultaneous with and opposed to the refractory phase, as the hypothesis of Fröhlich and Verworn would have it, but subsequent to and continuous with the refractory phase. It was this view of summation which Adrian and I[1] put forward. We suggested that summation of the type which we are now considering, which we called the summation of propagated disturbances, depended on the fact that after one nervous impulse has passed into a region of decrement in which it was eventually extinguished, the region traversed by that disturbance passed through a course of recovery which included a period of supernormal conduction; a second impulse, if so timed as to fall within the supernormal period, was conducted further, and so either passed through the region of decrement or made such passage possible for a successor which fell again in its supernormal period.

This hypothesis demands for its verification two lines of work. First it must be shown whether this type of summation is associated with the presence of some part of the nervous system which conducts with a decrement, and then it must be determined whether the impulses which give summation are those which are so timed that one will actually fall within the supernormal period left by its predecessor.

The second of these investigations is particularly important, because it may enable us to differentiate between the present hypothesis and that of Fröhlich and Verworn. If their hypothesis is correct, then summation will only be possible as long as the

[1] Adrian and Keith Lucas, "Journ. of Physiol.," p. 118, 1912.

second impulse occurs before the remainder of the electric response due to the first has subsided. If we may take Verworn's diagrams as substantially representing the hypothesis, it will also follow that a second impulse cannot sum after the refractory period due to its predecessor is over, for Verworn shows the relative refractory period as coterminous with the disintegration which constitutes the nervous impulse. If, on the other hand, the hypothesis which Adrian and I suggested is correct, then a second impulse in order to sum must fall at a time when the relative refractory period due to its predecessor is over and has been succeeded by the supernormal period. We may hope that on these lines experiment will give some indication as to which hypothesis is to be chosen.

CHAPTER X.

CONDUCTION IN JUNCTIONAL TISSUES.

ALONG many different lines of experiment evidence has slowly accumulated to show that on the path of conduction from motor nerve-fibre to skeletal muscle-fibre there lies a substance whose properties differ both from those of the nerve-fibre in the nerve-trunk and from those of the greater part of the muscle-fibre. The work of Waller,[1] Abelous,[2] and Santesson[3] established the fact that if nerve impulses are sent down a motor nerve with sufficient frequency, the neuro-muscular apparatus is brought into a state in which a stimulus applied to the nerve will cause no contraction of the muscle, whereas when applied directly to the muscle it will cause contraction. These observations, taken in conjunction with the failure of prolonged activity under like conditions to abolish conduction in the motor nerve-trunk,[4] have generally been regarded as proof that the "nerve-endings" are particularly subject to fatigue. In spite of the criticisms of Joteyko,[5] the evidence does seem to show that something which is not the nerve-fibre has failed to conduct, whereas the muscle is still able to contract.

Again, from the delay in conduction between nerve-trunk and muscle[6] we get a suggestion of the presence of some special con-

[1] Waller, "Brit. Med. Journ.," p. 135, 1885.

[2] Abelous, "Arch. de Physiol.," p. 437, 1893.

[3] Santesson, "Skand. Arch. f. Physiol.," v. p. 394, 1895.

[4] Bernstein, "Arch. f. d. ges. Physiol.," xv. p. 289, 1877; Wedensky, "Centralbl. f. d. med. Wissenschaften," p. 65, 1884; Bowditch, "Journ. of Physiol.," vi. p. 133, 1885; Maschek, "Stzber. d. k. k. Akad. Wien," iii. p. 109, 1887.

[5] Joteyko, "Dict. de Physiol. Richet," vi. p. 64, 1904.

[6] Bernstein, "Arch. f. (Anat. u.) Physiol.," p. 329, 1882; Tigersteadt, "Arch. f. (Anat. u.) Physiol.," Suppl., p. 111, 1885; Hoisholt, "Journ. of Physiol.," vi. p. 1, 1885; Boruttau, "Arch. f. (Anat. u.) Physiol.," p. 454, 1892; Asher, "Ztschr. f. Biol.," xxxi. p. 203, 1895.

ducting tissue, though Durig,[1] with good reason, doubts the interpretation which has been put on these observations.

The actions of curare as demonstrated by Bernard [2] and by Kolliker [3] at once suggests the presence of some special region in the path of conduction easily affected by the drug. The work of Kühne [4] and Pollitzer [5] brought new light into the matter by showing that after curare had made conduction from nerve-trunk to muscle impossible, there still remained in functional connection with the muscle in the region of entry of the nerves a substance which was more excitable than the non-neural region of the muscle-fibre. I showed that in the sartorius muscle of the frog and toad there was present in the region of nerve entry a substance which could be distinguished from the nerve-fibre of the trunk and from the non-neural part of the muscle-fibre by its response to electric currents of extremely short duration.[6] This substance still remained in functional connection with the rest of the muscle fibre after curare had acted sufficiently to make stimulation of the nerve-trunk ineffective. This work bears out the observations of Kühne, and forces us to recognise the existence of a special tissue, which lies on the muscular side of the region where curare blocks the nervous impulse, and is confined to the neighbourhood of the entry of the nerve into the muscular fibre.

Langley [7] showed that nicotine, in addition to preventing the conduction of the nervous impulse from nerve to skeletal muscle, causes a contraction of skeletal muscle in the fowl. The nicotine contraction is diminished by curare, and both effects go on after degeneration of the motor nerve. He concluded that this action of nicotine and curare could not be on the axon-endings; more-

[1] Durig, "Arch. f. d. ges. Physiol.," lxxxvii. p. 42, 1901.

[2] Bernard, "Leçons sur les effets des Substances Toxiques et Médicamentes," Paris, 1857.

[3] Kolliker, "Virchow's Archiv," x. p. 3, 1856.

[4] Kühne, "Arch. f. (Anat. u.) Physiol.," p. 477, 1860.

[5] Pollitzer, "Journ. of Physiol.," vii. p. 274, 1886.

[6] Keith Lucas, "Journ. of Physiol.," xxxiv. p. 372, 1906; xxxv. p. 103, 1906; xxxvi. p. 113, 1907.

[7] Langley, "Journ. of Physiol.," xxxiii. p. 374, 1905; "Proc. Roy. Soc. B.," xxviii. p. 170, 1906.

over, since nicotine and curare do not prevent the muscle from contracting on direct stimulation, he concluded that their action could not be directly on the contractile mechanism, and he suggested the term "receptive substance" for the thing on which they do act. Later he showed that nicotine, of a strength which does not affect the non-neural part of certain muscles, does cause contraction when applied locally in the region of the "nerve-ending,"[1] and continues to do so after degeneration of the motor nerve.[2] The result of these experiments is to give definite proof that in the region of entry of the nerve there is something whose physiological properties are not those of the rest of the muscle-fibre and are not those of the terminal nerve-fibres. To this substance Langley attributes the peculiarities which were formerly ascribed to "nerve-endings," such, for example, as the rapid fatigue of which we have already spoken. It is immaterial to the present argument what the trophic relations of this substance with nerve and muscle prove to be; the important point is that there is ample experimental evidence for its recognition. In order to avoid the implication of any hypothesis as to the nature of the tissue, I shall speak of it here simply as a "junctional tissue".

The problem before us now is to inquire into the peculiarities of conduction in junctional tissues, and to ascertain whether they are such as to enable an understanding of the phenomena of summation. It should be noticed that in all cases where the summation of nervous impulses has been observed in the peripheral nervous mechanism, there is certainly some kind of impaired conduction involved. I have already pointed out that the junctional tissue in the skeletal muscle of the frog is always in a condition approaching complete conduction-block when the summation is seen. This is true of fatigue, mild curarisation, removal of calcium, and treatment with acids. In the crayfish adductor preparation too the summation of singly ineffective impulses only occurs at a stage of fatigue which precedes com-

[1] Langley, "Journ. of Physiol.," xxxvi. p. 355, 1907; xxxvii. p. 187, 1908.
[2] *Ibid.*, p. 287, 1908.

plete block. But it cannot be asserted without further evidence that such conditions of impaired conduction are conditions of decrement. Nor is it possible owing to the small extent of the junctional tissue to show whether in such a condition an impulse can pass a short distance but not a long distance. The only evidence which we can get is the corollary of this, namely, that the junctional tissue can transmit a large nervous impulse but not a small one. We have already seen the evidence which shows that an artificially produced decrement in a nerve-trunk will transmit an early second impulse for a shorter distance than it will transmit a normal impulse travelling alone. Between the end of the absolute refractory period and the first return to normal there is a phase in which the earlier the second impulse comes the less far will it travel in the narcotised nerve. This observation we interpreted as meaning that a nervous impulse following close on the heels of another resembles in its ability to be conducted one which has already travelled some distance through a region of decrement. In both cases the impulse is in such a state that it cannot travel so far in a decrement without extinction as can a normal impulse. By timing a second impulse so that it is in this way reduced we can test any artificial decrement. If a very early second impulse can pass, the decrement is slight; if the second impulse must be put later in order that it may pass, the decrement is greater. I have used this method in order to get a measure of the decrement undergone by an impulse passing along nerve treated with alcohol.[1] Now in this respect the junctional tissue in various stages of fatigue or impairment behaves towards the nervous impulse just as does the artificial decrement in the nerve-trunk. Some years ago I noticed that when a nerve-muscle preparation was stimulated in the nerve with two stimuli, the second stimulus might fail to affect the muscle although it sent a nervous impulse down the nerve.[2] For example, if the second stimulus fell ·0128 of a second after the first, a second electric response could

[1] Keith Lucas, "Journ. of Physiol.," xlvi. p. 470, 1913.
[2] *Ibid.*, xliii. p. 55, 1911.

be seen in the capillary electrometer connected to the nerve, but no increase of the muscular contraction occurred until the interval between stimuli exceeded ·0151 sec. This result in itself might mean no more than that the nerve-fibres leading to the gastrocnemius had a longer refractory period than other fibres in the sciatic nerve. Such an interpretation, however, fails to account for another observation, namely, that a second stimulus which fell just too early to cause an increase of muscular contraction did set up a refractory period in the nerve-fibres leading to the gastrocnemius.[1] This was evident since such a stimulus prevented a later stimulus from affecting the contraction of the muscle. The presence of a refractory period in the nerve is proof that a nervous impulse has passed; as Adrian[2] showed later, the refractory period in this experiment can be found in parts of the nerve other than that directly subjected to the stimulus, so that the actual propagation of a nervous impulse from the seat of stimulation is beyond question.

The outcome of these experiments is to show that when conduction from nerve to muscle is certainly not greatly impaired by fatigue or damage, a normal nervous impulse can pass through and affect the muscle, but an impulse which has gone down the nerve close after another cannot do so. There is in fact a complete analogy between the behaviour of the junctional tissue and that of an artificial decrement in the nerve-trunk towards a second impulse following another at various intervals of time. Not only does the junctional tissue refuse to transmit an early second impulse, but, as I was able to show,[3] if the preparation has been slightly fatigued or left in Ringer's solution for a number of hours, the second impulse must be set at a longer interval after the first if it is to pass through and affect the muscle. This resembles the behaviour of a given length of nerve which is exposed for varying lengths of time to alcohol; the longer the alcohol has acted, the greater must be the interval at

[1] Keith Lucas, "Journ. of Physiol.," xliii. p. 65, 1911.
[2] Adrian, "Journ. of Physiol.," xlvi. p. 395, 1913.
[3] Keith Lucas, "Journ. of Physiol.," xliii. p. 70, 1911.

which the second impulse follows the first if it is to pass through without extinction.[1] The mere fact that the earlier second impulse cannot pass through where the single impulse can is capable of two explanations. The impulse is both early and therefore reduced. Because it is reduced it would fail in conduction if the junctional tissue presented a decrement; because it is early it would fail if the junctional tissue had a longer refractory period than the nerve. In the case of the nerve treated with alcohol the evidence shows without doubt that the early second impulse fails because the nerve conducts with a decrement. In the first place the longer the stretch of narcotised nerve to be traversed the later must the second impulse follow if it is to avoid extinction, and this effect a prolonged refractory period cannot explain; and beyond this I have shown[2] that at the stage at which alcohol produces this effect the refractory period of the narcotised nerve is certainly not prolonged. The behaviour of the junctional tissue then copies that of an undoubted decrement, but might also be explained on the supposition that the junctional tissue has a prolonged refractory period. Bramwell and I[3] tried to decide between the two alternatives by experiment, but Adrian has since found that our supposed proof rested on measurements which were not sufficiently exact, and in reality the method which we adopted gives no answer to the question. It seems that there is no direct experimental method at present by which the question can be settled. It can only be said that no fact has yet been found which is not in agreement with the supposition that the junctional tissue is a region of decrement; this hypothesis makes it easy to understand how the junctional tissue fails so readily under any abnormal treatment to conduct a single full-sized nervous impulse, whereas the supposition of a long refractory period covers only the cases in which it is a second impulse which fails to pass. Moreover, the supposition of a decrement gives, as we shall see, a simple

[1] Adrian and Keith Lucas, "Journ. of Physiol.," xliv. p. 96, 1912.
[2] Keith Lucas, "Journ. of Physiol.," xlvi. p. 470, 1913.
[3] Bramwell and Keith Lucas, "Journ. of Physiol.," xlii. p. 495, 1911.

explanation of the phenomena of summation at the junctional tissue.

Lapicque has developed a view of conduction from nerve to muscle which does not agree with that presented here. He regards the junction of nerve and muscle as immediate, and states that there are not good grounds for the conception of a "special organ interposed between the nervous conductor and the muscle".[1] On the ground of researches made by Mme. Lapicque and himself on the action of curare,[2] veratrin,[3] and strychnin,[4] he finds that conduction fails between nerve and muscle when the one tissue is made slower or more rapid than the other in its excitatory process. This conception recalls the observation of Engelmann[5] that in muscle-fibres conduction fails between a part which is cooled and one which is warmed, or between a part treated with veratrin and a part in salt solution. Lapicque finds in the hypothesis that failure of conduction is due to "heterochronism" of the nerve and muscle a reason for dispensing with any intermediate tissue, but he shows no ground for rejecting the evidence already adduced to show the existence of junctional tissues. It should be noticed also that he has measured the effects of his drugs on the local excitatory process of nerve and muscle, whereas his hypothesis related to the rapidity of the process involved in conduction. It may be, as he says,[6] that the two processes vary together, but the evidence for this is indirect. In any case, if difference of time relations between adjoining tissues is the cause of failure of conduction, the failure may be due to the impulse undergoing a decrement as it passes through the region of transition.

The experiments described in this section constitute a small beginning of knowledge about conduction in peripheral junctional tissues, but there is still very much to be learned. It

[1] Lapicque, "C. R. Soc. de Biol.," lxv. p. 733, 1908; lxviii. p. 1007, 1910.
[2] M. and Mme. Lapicque, "C. R. Soc. de Biol.," lx. p. 991, 1906.
[3] *Ibid.*, lxxii. p. 283, 1912.
[4] Mme. Lapicque, *ibid.*, lxii. p. 1062, 1907.
[5] Engelmann, "Arch. f. d. ges. Physiol.," lxii. p. 400, 1896.
[6] Lapicque, "C. R. Soc. de Biol.," lxiii. p. 787, 1907.

would seem probable that conduction across the synapse is of the same type.[1] The failure of single impulses on the afferent side to evoke a reflex response certainly suggests that the resistance to conduction at a synapse may be an expression rather of decrement than of long refractory phase, but much more work is needed before we can say that the resemblance is more than superficial. I shall not discuss the point further now because our study of summation and inhibition will reveal many points of similarity between the synapse and a region of decrement. Recent work on the heart again brings to light a series of phenomena, particularly those of partial and complete heart-block, which suggest an analogy between conduction with a decrement and conduction through the auriculo-ventricular bundle. It is evident that the bundle often behaves like a region of decrement in transmitting impulses which come to it with a moderate frequency, while refusing one which comes too early. Mines[2] has suggested in this connection that the A-V bundle may conduct with a decrement, particularly when treated with solutions on the acid side of normal. Another analogy between the auriculo-ventricular bundle and the junctional tissue of skeletal muscle is the failure of conduction which follows a lowered concentration of calcium.[3]

The conclusion which I would draw is that the supposition of a decrement in conduction is the only hypothesis yet put forward which gives an account of all the known phenomena of conduction in the junctional tissue between nerve and skeletal muscle. This description will therefore serve until it shall be contradicted by new observations, and we may proceed to inquire whether the second question which was foreshadowed in the last chapter, that of the time-relations between nervous impulses which give summation, is also to be answered in conformity with our hypothesis of summation.

[1] Sherrington, "Intergrative Action of the Nervous System," p. 16, 1906.

[2] Mines, "Journ. of Physiol.," xlvi. p. 349, 1913.

[3] Locke, "Centralbl. f. Physiol.," viii. p. 167, 1894; Mines, "Journ. of Physiol.," xlvi. p. 188, 1913.

CHAPTER XI.

THE TIME INTERVAL AT WHICH TWO NERVOUS IMPULSES GIVE SUMMATION.

You will remember that if the hypothesis of Fröhlich and Verworn is correct, summation will occur only when the second impulse falls within the relative refractory period of the first; but on the hypothesis that summation is the expression of a supernormal period it should occur only if the second impulse comes after the relative refractory period is over.

Adrian and I tried two methods for obtaining an idea of the

Fig. 16.

time interval at which two impulses will sum.[1] One was to fatigue the junctional tissue of a sciatic gastrocnemius preparation by tetanising the nerve until a single stimulus applied to the nerve gave no contraction of the muscle. When this stage was reached we tried at what frequency the impulses must be sent down the nerve if they were to sum and cause a contraction.

[1] Adrian and Keith Lucas, "Journ. of Physiol.," xliv. p. 84, 1912.

Fig. 16 shows an observation of this kind. First there are shown movements of the stimulation signal and of the recording lever made on the stationary drum to indicate that the one record is truly in time register with the other. The drum is then started, and stimuli 0·5 sec. apart cause no contraction of the muscle; stimuli at 0·1 sec., 0·05 sec., and 0·12 sec. intervals do cause contraction, and it should be noticed that these contractions do not begin until several stimuli have passed; after this, stimuli at 0·5 sec. interval are again without effect, and 0·05 sec. are again successful, the delay of response being this time very clear. So far we see that at 16° C. summation is readily obtained if the interval between stimuli is as great as 0·1 sec. but fails when the interval reaches 0·5 sec.

The second method consisted in determining the time relations of the effect described by Samojloff. It will be recalled that Samojloff[1] found that the second electric response in a muscle might be greater than the normal value in resting muscle if the interval separating the two responses fell within certain time limits. Adrian and I showed that the effect was only obtained when the impulses had to pass across the junctional tissue before reaching the muscle, and we also showed that the effect was due to better conduction in the nerve and not to increased excitability. We found that the second electric response was larger than the first if the interval between the stimuli was greater than 0·02 sec., and that the effect was at its maximum at about 0·035 sec. in the sartorius and 0·05 sec. in the gastrocnemius (see Figs. 14 and 15). These experiments gave us a preliminary indication that impulses would sum successfully if they were separated by an interval of about 0·05 sec., but the difficulty we met was that we could not correlate this time with the course of recovery of the tissue concerned. It is clear enough that in the nerve the relative refractory period is fully over even at 0·02 sec. after the passage of an impulse, but it is probably conduction in the junctional tissue between nerve and muscle

[1] Samojloff, "Arch. f. (Anat. u.) Physiol.," Suppl., p. 1, 1908.

which will determine whether the impulse reaches the muscle, and we cannot tell how long the refractory period of that tissue was in these experiments.

The results were, however, sufficiently suggestive to encourage a further attempt, and I have since made experiments of a similar type on the neuro-muscular apparatus of the claw in the crayfish.[1]

Richet's[2] experiments had shown how easily the crayfish claw came into that condition in which a single stimulus applied to the nerve had no apparent effect, whereas repeated stimuli were successful. Lapicque[3] pointed out that this case was not one of local summation under the electrodes. I repeated Richet's observations, and found that, as Lapicque had suggested, the summation was equally well seen if the successive stimuli were applied to different points on the nerve. The case was therefore without doubt one in which the summation was between successive nervous impulses. The great advantage which the crayfish claw offers for this work is the long duration of the state in which summation can easily be obtained while a single impulse is ineffective. For a time as long as forty minutes two stimuli properly timed will always cause a contraction, whereas one alone has no visible effect. During this period I was able to determine the range of time intervals within which the second impulse must fall if it was to produce summation, and the observations could be checked over several times in reversed order of sequence, so that progressive errors were eliminated.

Preliminary observations were made in which, when the single stimulus gave no contractions at all, two stimuli were sent in at various intervals of time. It was evident that the two nervous impulses summed and caused a contraction even if they were separated by as long a time as ·04 sec. The device which I was using for timing the two stimuli did not allow a longer interval than this. I then tried to map out a curve showing the size of

[1] Keith Lucas, "Journ. of Physiol.," li. p. 1, 1917.
[2] Richet, "Travaux du laboratoire de M. Marey," p. 97, 1877.
[3] Lapicque, "Livre jubilaire Ch. Richet," 1912.

contraction produced by the second impulse when it was started at various intervals after the first. There was some complexity introduced into this investigation by the fact that the neuro-muscular system of the claw adductor contains two kinds of nerve-fibres leading to two kinds of muscle-fibres. The one system leads to a slow contraction of the adductor muscle, and the other to a twitch. Without going more closely into the evidence for this statement, I may say here that the double system in the crayfish resembles that whose presence I demonstrated in the claw of the lobster in 1907.[1] In consequence of the presence of two systems one often gets a complex curve relating the contraction produced by the second impulse to the interval between the two impulses. Sometimes, however, the quicker system does not show itself, and for the sake of simplicity I shall now speak only of such cases.

As the interval between the stimuli is increased the contraction (which, it should be remembered, is due wholly to the second stimulus) grows rapidly larger, and reaches a maximum when the interval is about ·015 sec., then it decreases slowly as the second stimulus occurs later. The variation of height of the contraction is probably a statistical measure of the success of the second impulse, depending on the number of fibres which successfully conduct through the junctional tissue. Fig. 17 shows in the upper compartment the curve relating the height of contraction to the interval between stimuli from its commencement until it has passed its culmination. From such experiments I conclude that the second impulse sums with the first most effectively when it follows at an interval between ·01 and ·015 sec., and ceases to sum when it follows at an interval of about ·05 sec.

But how are these times at which the two impulses sum related to the refractory period of the tissues through which the impulses are conducted? If the course of the refractory period in the nerve is mapped out in the ordinary way, with the precaution that the second stimulus shall not fall on the seat of the first

[1] Keith Lucas, "Journ. of Physiol.," xxxv. p. 326, 1907.

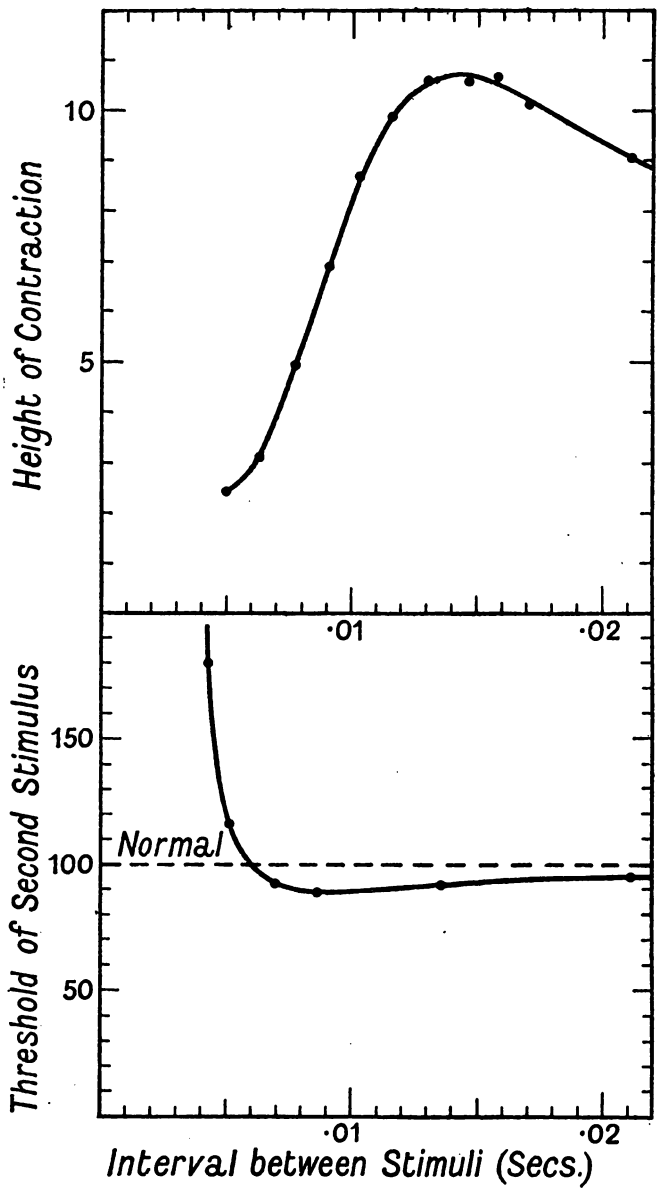
Height of Contraction
10
5
·01
·02
Threshold of Second Stimulus
150
Normal
100
50
·01
·02
Interval between Stimuli (Secs.)

FIG. 17.

stimulus, the relative refractory phase is found to end at about ·006 sec. and to be succeeded by a well-marked supernormal phase which is still quite large at ·02 sec. In the present experiment the recovery curve was determined just before the observations on summation were made, and while the first stimulus was still causing a barely visible contraction of the muscle. There is evidence that in the time interval which succeeds this and is occupied in the observations on summation the recovery curve undergoes no important change. I have placed the curve of returning excitability in the figure below the curve of contractions, and the time scale is the same for both. The relative refractory phase is over long before summation has even culminated; in fact the summation curve comes to a maximum not earlier than the period of greatest supernormality. Here, as in the case of summation in the nerve-muscle preparation already discussed, we have to do with the recovery curve of the nerve, whereas we really want to know whether summation occurs before or after the relative refractory period ends in the tissue in which summation takes place.

The work of Adrian[1] on the recovery curve of the frog's motor nerve, however, gives a valuable method by which we may tell, from the recovery curve obtained at any point on a motor nerve, not only the condition of the nerve at that point, but also whether the impulse encounters a region of prolonged refractory phase or of decrement on its way to the muscle. Adrian found that in a preparation in which the recovery curve of the nerve is of the simple type shown in Fig. 7, page 38, local cooling of a part of the nerve between the seat of excitation and the muscle produces a profound change in the curve. Fig. 8 showed as a dotted line the recovery curve when all the nerve was at 16° C. and as a full line the results obtained while a portion traversed by the nervous impulse was at 3° C., and the rest still at 16° C. When the local cooling was in action no impulse started in the nerve earlier than ·0068 sec. after a predecessor could affect the muscle, whatever the strength of stimulus used to provoke it,

[1] Adrian, "Journ. of Physiol.," xlvi. p 384, 1913.

whereas when the nerve was all at 16° C. a second impulse started after an interval of only ·0027 sec. could already pass to the muscle and cause an increased contraction. By experiments on these lines Adrian showed that the recovery curve gave information about two points; from the smooth part of the curve it could be seen how the local excitability of the nerve under the electrodes recovered, and from the straight vertical line it could be ascertained whether there was some difficulty of conduction preventing an early second impulse reaching the muscle though the nerve was recovered enough to allow a second impulse to be started.

Now on looking back at the recovery curve of the crayfish nerve (Fig. 17) we see that it is of the smooth type, which means that the controlling factor which determined whether the second impulse reached the muscle was whether the nerve itself was recovered enough to allow a second impulse to be started; if a second impulse was started at all it affected the muscle. This state of things is not compatible with the supposition that the second impulse encountered on its way to the muscle a region whose refractory phase was greatly longer than that of the nerve. From the experiments on the time relations of summation it has been shown that summation still occurs when the interval between the impulses sent down the nerve is about ten times as long as the duration of the relative refractory phase in the nerve. If we are to suppose that summation is obtained only when the second impulse occurs before the end of the relative refractory phase of the junctional tissue in which summation takes place, we must postulate a refractory period in that tissue ten times as long as that of the nerve. Such a supposition is difficult to reconcile with the facts already described.

These facts establish a strong presumption that the nervous impulses do sum when the second arrives after the relative refractory period of the first is over, and therefore that the mechanism of summation cannot be that which Fröhlich and Verworn have suggested. In fact both in the crayfish and in the frog the interval at which two impulses will still sum fits more easily

with the hypothesis that summation depends on the development of a supernormal period after the refractory period is over. At the same time the investigation is not yet completed, and I cannot regard the question as settled until future work shall give us more exact knowledge of the time relations of recovery in the tissues through which the nervous impulse has to pass on its way to the muscle. The point which I do emphasise is that we have now a road open not to mere speculation about the nature of summation in the nervous system, but to quantitative measurement of the phenomenon as it occurs in certain simple cases, and so to the verification or rejection of such hypotheses as have been proposed. Given the hypotheses and the means of testing them the rest is merely a matter of work. When a satisfactory explanation has been found which accords with all the tests which can be made on the relatively simple case of summation of nervous impulses in peripheral tissues, then it will be soon enough to examine more closely the analogy which we have already seen to exist between this type of peripheral summation and summation in the reflex arc. One point should be clearly recognised even at this early stage, that if the hypothesis of summation which Adrian and I have put forward does prove to be substantially correct, there are two factors essentially engaged in it. There is not only the normal course of recovery of the conducting tissues, but there is also the presence of tissues which conduct with a decrement, and therein, possibly, lies the importance of the synapse in summation. When we come to consider Inhibition we shall see that there also regions of decrement may play an essential part.

CHAPTER XII.

THE PHENOMENA AND THE EXPLANATION OF "APPARENT INHIBITION" IN PERIPHERAL TISSUES.

WE have seen that successive nervous impulses so timed as to fall each in the supernormal phase succeeding its predecessor, may give rise to a phenomenon closely resembling and perhaps accounting for the summation observed in the central nervous system. In just the same way it seems possible that inhibition might arise if impulses occurred with greater frequency, so that each arrived while the tissue had not yet recovered from the impaired conduction which constitutes the refractory phase. The exact circumstances under which such an effect might occur need to be examined critically. We may proceed, as in the case of summation, by studying first the phenomena as they are seen in peripheral tissues, and elucidating the mechanism of the peripheral effect before inquiring whether it is a true counterpart of central inhibition.

Schiff[1] was the first to describe an occurrence in the motor nerve and skeletal muscle of the frog which recalls certain features of inhibition. If a motor nerve is stimulated with rapidly repeated stimuli for several minutes the contraction of the muscle dies down and presently disappears. When this stage is reached the stimuli are stopped for a few seconds; when they are started again the muscle responds with a single twitch only, and is at rest again as long as the stimuli are continued. Moreover, as long as the rapid stimuli are continued no contraction is evoked by single stimuli applied to the nerve at a point nearer the muscle; soon after the rapid stimuli are stopped such single

[1] Schiff, "Lehrbuch der Physiol. des Menschen," i. p. 184, 1858-59; "Gesammelte Beiträge zur Physiol.," i. p. 633, 1894.

stimuli become effective. Wedensky[1] studied in greater detail the conditions under which the frequent stimuli gave absence of contraction. He showed that the effect appears when the stimuli are made either stronger if of sufficient frequency, or more frequent if of sufficient strength; it is obtained only when the nerve is excited, not when the stimuli are applied directly to curarised muscle, yet does not depend, as Schiff thought, on exhaustion of the nerve, for the nerve continues to transmit impulses. It was already known from Schiff's work that during the absence of contraction due to rapid stimulation of the nerve the muscle rested and recovered,[2] so that the inference followed that the failure of the impulses depended on a failure of conduction in the junctional region between nerve and muscle.

Later Wedensky,[3] extending some earlier observations[4] on narcosis, added the important observation that in a nerve-muscle preparation, in which there has been no preliminary fatigue induced, the effect can be obtained if a stretch of nerve between the seat of stimulation and the muscle is subjected to any treatment which impairs conduction. Local narcosis, treatment with strong solutions of sodium chloride, heating to 40° or 45° C., or the application of a strong constant current will provoke the necessary condition. Wedensky[5] regarded these agents as reproducing the effect of the neuro-muscular junction, and spoke of them as making "artificial nerve endings". Hofmann[6] about the same time showed, as did also Wedensky, that phenomena of essentially the same kind are seen if the preparation is not fatigued but treated with weak curare or nicotine, whose effect in stronger doses is known to be a complete suspension of conduction from nerve to muscle.

The essential conditions of the apparent inhibition were clearly defined by these researches; they may be summed up as

[1] Wedensky, "Arch. f. d. ges. Physiol.," xxxvii. p. 69, 1885.

[2] Schiff, "Lehrbuch der Physiol. des Menschen," i. p. 189, 1858-59; see also Wedensky, "Arch. de Physiol," Ser. v. iii. p. 687, 1891.

[3] Wedensky, "Arch. f. d. ges. Physiol.," c. p. 1, 1903.

[4] *Ibid.*, lxxxii. p. 134, 1900. [5] *Ibid.*, c. p. 116, 1903.

[6] Hofmann, *ibid.*, xciii. p. 186, 1903; xcv. p. 484, 1903.

a sufficient strength and frequency of stimuli applied to the nerve, and a region of impaired conduction between the seat of stimulation and the muscle. The problem is to understand how these conditions lead to an absence of contraction in the muscle, and to a failure of single stimuli applied between the seat of frequent stimulation and the region of impaired conduction.

The explanation first offered by Schiff, that the nerve became exhausted and ceased to transmit impulses, need not be considered; Wedensky's evidence, that the nerve continues to show electric responses after the muscle has ceased to contract, disposes of this possibility. Wedensky himself proposed in his first study of the phenomena that each impulse fell within the refractory period of its predecessor and so produced no visible effect. He afterwards abandoned this idea, and as a result of his experiments on local narcosis came to regard the state of the nerve in which the phenomena occur as one of auto-excitation.[1] This view was supported partly by the fact that in the neighbourhood of the narcotised region excitability was abnormally high, and partly by the presence of a current between normal and narcotised nerve like in direction to that between normal and injured nerve. Since this current was a steady one the auto-excitation or "Parabiosis" was regarded as a steady state in distinction to the ordinary waves of excitation. Waves of excitation coming from outside were supposed to add themselves to this steady excitation. In so far as a part of the nerve which has the same electric sign as excited nerve may be regarded as in a state of excitation, this conception expresses the facts. The phenomena are essentially those dealt with a year later by Boruttau and Fröhlich,[2] which we have considered already in connection with the problem of summation. To my mind this way of looking at the phenomena does not really present in terms of the already known phenomena of conduction an explanation of the failure of impulses to pass through and reach the muscle.

[1] Wedensky, "Arch. f. d. ges. Physiol.," c. p. 64, 1903.
[2] Boruttau and Fröhlich, "Arch. f. d. ges. Physiol.," cv. p. 461, 1904.

Hofmann[1] offered a very different account. After the passage of a nervous impulse there is conduction-fatigue, as Englemann[2] showed in his experiments on the ureter. This fatigue may cause the impulses which follow at sufficient frequency to undergo a decrement, probably not in the nerve trunk, since this he supposed to be incapable of fatigue, but in the nerve-ending; there the impulses may be reduced until they are either extinguished or made too small to affect the muscle. The main objection to this hypothesis is that, though it accounts for the effect of an increased frequency of stimuli, it fails to explain why strong stimuli of a given frequency should produce absence of contraction in the muscle, whereas weak stimuli of the same frequency do evoke contraction. To get over this difficulty Hofmann was obliged to postulate that the stronger stimuli set up more intense nervous impulses which left behind a different refractory state in the nerve-ending. We know from recent work, already described above, that such a supposition is contrary to experimental results.

In the same year Fröhlich also attacked the problem. He showed[3] that when a portion of a nerve between the seat of excitation and the muscle was narcotised or asphyxiated, two stimuli must be separated by a longer time interval than was required in the normal nerve if the second was to affect the muscle and produce a summated contraction. This he interpreted to mean that asphyxia or narcosis prolonged the refractory period of the nerve. He then proposed, as an explanation of Wedensky's observations on locally narcotised nerve, that when the refractory phase is thus prolonged "only the first stimulus appears effective, the second stimulus falls in the refractory phase of the first, and hence is ineffective". There are several difficulties about this hypothesis. In the first place, it is doubtful whether asphyxia and narcosis do really prolong the refractory period of the nerve in the sense that they make its

[1] Hofmann, "Arch. f. d. ges. Physiol.," ciii. p. 291, 1904.
[2] Englemann, "Arch. f. d. ges. Physiol.," ii. p. 271, 1869.
[3] Fröhlich, "Ztschr. f. allg. Physiol.," iii. p. 468, 1904.

recovery slower. I have shown[1] that alcohol calls for an increase in the interval between stimuli which can produce a summated contraction, as in Fröhlich's experiment, not because it prolongs the refractory phase of the nerve, but because it makes the nerve conduct with a decrement. The stimuli must be placed at a greater interval in order that the impulse set up by the second may be not so much reduced and hence may face the decrement in the narcotised nerve without extinction; this takes place while the refractory period of the nerve is still unaltered. Whether there is any true prolongation of the refractory period when the nerve is asphyxiated is a question which is not yet settled.

But apart from this question it is difficult to see how such a mechanism as Fröhlich suggests would lead to extinction of impulses in the narcotised part of the nerve. The refractory phase is a consequence of the nervous impulse,[2] and if the second of two stimuli falls in the refractory phase of the first and consequently is ineffective in the sense of setting up no nervous impulse, then it will also set up no refractory phase, and a third stimulus will again set up a nervous impulse. In this way the falling of successive stimuli in the refractory phase of their predecessors cannot by itself continuously prevent the setting up of nervous impulses.

Considerations of this sort led me to examine experimentally the effect of a stimulus falling within the refractory phase of its predecessor.[3] I found first that in the sartorius muscle of the frog a second stimulus so timed as to fall just within the refractory phase of its predecessor, and consequently to cause no second electric response in the muscle, does not reduce the electric response set up by a stimulus which falls just outside the same refractory phase. In such a homogeneous tissue then the second stimulus either produces a response of its own or else does

[1] Keith Lucas, "Journ. of Physiol.," xlvi. p. 470, 1913.

[2] Gotch, "Journ. of Physiol.," xl. p. 267, 1910; Bramwell and Lucas, "Journ. of Physiol.," xlii. p. 495, 1911.

[3] Keith Lucas, "Journ. of Physiol.," xliii. p. 46, 1911.

not prolong the refractory state; consequently a complete absence of effect cannot be produced by rapidly repeated stimuli. If, however, the stimuli are applied to the motor nerve and not to the muscle, a new factor comes in. Boycott[1] showed that there is a least interval at which two stimuli applied to the nerve will both affect the muscle, and he regarded this interval as a measure of the "critical interval" or refractory period of the nerve. Such an interpretation was supported by the general agreement of Boycott's results with the values found by Gotch and Burch[2] for the least interval at which two stimuli would both produce electric responses in the nerve itself. I found, however, on making both observations on the same nerve, that the interval required to produce a summated contraction in the muscle was normally about 20 per cent greater than that required to produce a double electric response in the nerve. This fact is apparently an expression in its simplest form of the phenomenon studied by Wedensky,[3] when he showed that if rapidly repeated stimuli are applied to a motor nerve the number of impulses heard in a telephone attached to the nerve is greater than that heard in a telephone attached to the muscle. It followed that a second stimulus succeeding a first within a certain range of time-intervals must set up a second nervous impulse which did not produce a contraction in the muscle. I then observed that if a second stimulus was so timed as to fall really within the refractory period of the nerve it did not reduce the effect produced on the muscle by a later third stimulus. If, however, the second stimulus did set up a second impulse in the nerve too early to affect the muscle, then the effect of the third stimulus, which otherwise appeared as an additional electric response or contraction of the muscle, was either reduced or abolished. These two experiments are shown in Figs. 18 to 21. Fig. 18 shows the double electric response of the gastrocnemius muscle to two stimuli sent into the nerve at the time interval shown;

[1] Boycott, "Journ. of Physiol.," xxiv. p. 144, 1899.
[2] Gotch and Burch, "Journ. of Physiol.," xxiv. p. 410, 1899.
[3] Wedensky, "Arch. f. d. ges. Physiol.," c. p. 115, 1903.

in the next figure there is interpolated between these a stimulus

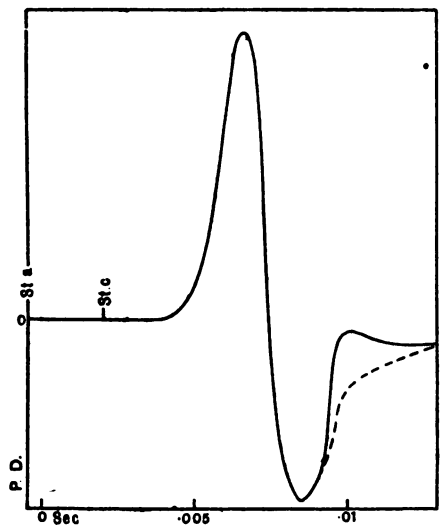

FIG. 18.

too early to set up an impulse in the nerve, and the result is that this stimulus slightly strengthens the effect of the succeeding

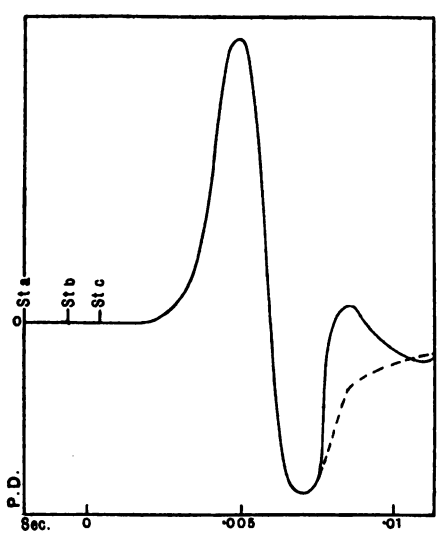

FIG. 19.

stimulus, making the second electric response larger. In Fig. 20 there is shown again the double response to two stimuli; in

Fig. 21 a stimulus is interpolated at such a time that it does set up a second impulse in the nerve but is too early to cause a

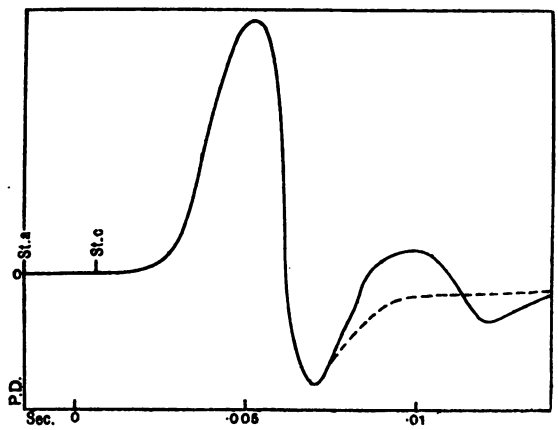

FIG. 20.

response of the muscle, and the result is that the second response previously caused by the succeeding stimulus disappears.

These experiments give a key to the understanding of the phenomena observed by Schiff and Wedensky. We see that the

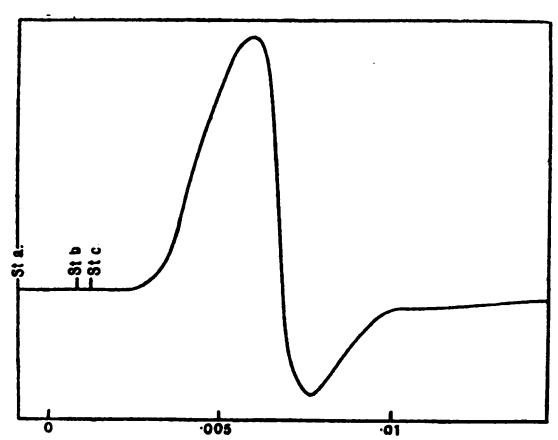

FIG. 21.

condition for the absence of effect of successive stimuli on the muscle is that the second should set up in the nerve an impulse which is too early to affect the muscle; this early impulse prevents a later impulse from affecting the muscle. The interpreta-

tion of the fact is simple when we recall the observation described in a former section, that an early second impulse resembles one which has passed some way through a region of decrement. The second stimulus falls at such a time that its impulse passes down the nerve in this reduced condition. On reaching the junctional tissue it cannot pass through, probably because that tissue conducts with a decrement. The reduced impulse has, however, passed along the nerve and left there a new state of impaired conduction; consequently the third impulse, if suitably timed, will also be propagated in a reduced condition and fail to pass the decrement. This state of things can be continued as long as the stimuli fall on the nerve with the appropriate frequency.

Before considering whether this explanation fits all the observed facts, I may point out how it differs from those of Hofmann and Fröhlich. Hofmann regarded the nerve as incapable of fatigue, and consequently supposed that the refractory period concerned must be in the "nerve-ending"; we know now that incompletely recovered nerve conducts a reduced impulse, so that the present explanation makes the incomplete recovery of the nerve itself account for the impulse being small when it arrives at the junctional tissue. This difference avoids, as will presently appear, the necessity, to which Hofmann was driven, of supposing that stronger stimuli send larger impulses down the nerve. The part played by the junctional tissue in Hofmann's explanation was that of a prolonged refractory phase; in this explanation it is a decrement. This difference is important not only because, as we have seen elsewhere, the junctional tissue is more probably a region of decrement than one of prolonged refractory phase, but also because alcohol, which reproduces all these effects of a junctional tissue, produces a decrement and not a prolonged refractory phase. Fröhlich's explanation also put the burden on the refractory phase of the narcotised region, whereas in the present explanation it is the refractory phase of the normal nerve and the decrement of the narcotised region which come into play.

It is obvious how on this view the greater frequency of stimuli applied to the nerve may favour the absence of response in the muscle. The more frequent the stimuli the more frequent will the impulses be in the nerve, and consequently each impulse will travel in less completely recovered nerve and be more reduced and less able to face a decrement without extinction. The effect of an increase of strength of stimuli is at first glance less obvious. I suggested[1] that this effect might be explained on the ground that in the course of the relative refractory phase the excitability of the nerve recovers gradually, and in consequence the stronger the stimuli the sooner will they be able to set up another nervous impulse. This might result in strong stimuli of given frequency setting up more frequent impulses than weak stimuli of the same frequency, so that increase of strength would be only a special case of increase of frequency. Adrian[2] tested this suggestion experimentally, and found that it was in agreement with experimental observation. In fact he was able by mapping out the course of returning excitability in a nerve to foretell the relation between the strength and the frequency of stimuli which would give absence of contraction in a given preparation and to show that his forecast was correct.

It is evident that if impulses are passing down a nerve with sufficient frequency to produce this effect, the addition of more to their number will not cause contraction of the muscle. Thus in Schiff's original observation slowly repeated stimuli applied to the nerve between the seat of the rapid stimulation and the muscle ceased to cause contraction when the rapid stimuli were in action.

The explanation which I have offered accounts also for a distinctive feature of all cases in which the phenomena of Schiff and Wedensky is observed, namely, that there is present some condition which if pushed a little further leads to a total failure of conduction. The heating of nerve above 40° C., the electrotonic block, alcohol, absence of oxygen, as well as curare and

[1] Keith Lucas, "Journ. of Physiol.," xliii. p. 80, 1911.
[2] Adrian, "Journ. of Physiol.," xlvi. p. 401, 1913.

nicotine acting on the junctional tissues, all suspend conduction soon after they have produced the effect. Failure of conduction is commonly a step beyond conduction with a decrement, whereas it cannot be maintained that all these conditions cause a prolonged refractory phase. On this view then the phenomena of absence of contraction with rapid stimulation, or "apparent inhibition," are accounted for in terms of four properties of the excitable tissues which have already been examined and verified in earlier parts of these lectures :—

(1) That a nervous impulse following close on a predecessor resembles one which has passed for some distance through a region of decrement.

(2) That the excitability of nerve to an external stimulus returns gradually to normal after an impulse has passed.

(3) That narcotised nerve and probably also fatigued junctional tissues conduct with a decrement.

(4) That the intensity of the impulse set up in a nerve is independent of the strength of the stimulus which evokes it.

CHAPTER XIII.

CENTRAL INHIBITION.

WE set out to inquire whether the elementary phenomena of conduction in simple tissues could give a satisfactory basis for the understanding of conduction in the reflex arc. We have seen that two of the most important phenomena of reflex conduction, namely, summation and inhibition, can be reproduced in the isolated muscle-nerve preparation, and that in this case they depend on a very simple mechanism. Impulses which are timed so that each falls in the supernormal phase of recovery left by its predecessor are more readily conducted through a region of decrement than is an impulse of normal intensity. Consequently a series of impulses so timed will be conducted successfully when a single impulse will fail. This is the mechanism of peripheral summation. On the other hand, a series of impulses timed so that each falls in the phase of subnormal recovery will be less able to travel than an impulse of normal intensity. A series timed in this way will be extinguished in a region of decrement through which a single impulse can pass and they will also prevent the passage of other impulses which were formerly successful. This constitutes the mechanism of "apparent inhibition". The two processes depend simply on the normal recovery phenomena in nerve and the action of a region of decrement in extinguishing impulses of small intensity. We have already given reasons for the belief that regions of decrement are normally present in the junctional areas of the central nervous system, and therefore we have in the reflex arc all the conditions necessary for the production of inhibition and summation by the simple mechanism we have described. In fact if we consider the complications which are introduced when the impulse

has to pass through several relays of conductors, it will be clear that the most varied possibilities are opened up without introducing any assumptions which have not been proved in the case of peripheral conduction.

As an instance of this we may take the mechanism of reciprocal innervation. The facts to be explained are that a series of stimuli applied to an afferent nerve X (Fig. 22) produces a contraction in the muscle A and a simultaneous inhibition of tone in the antagonistic muscle B, and that stimuli applied to another nerve Y have the opposite effect, causing contraction in B and inhibition in A. Let us suppose that in the nerves X and Y recovery takes place at such a rate that 100 impulses can be conducted in one second without very much reduction in intensity. X is in communication with the muscle A by two relays X_1X_2 and X_2X_3. Suppose the tract X_1X_2 to have a longer refractory period, so that every other impulse from X arrives at a time when X_1X_2 cannot conduct at all. The result will be that only 50 impulses a second will pass into X_2X_3. Now the nerve Y has a branch passing directly to X_2 without the intervention of the tract X_1X_2. Consequently Y will send 100 impulses to X_2 whereas X sends only 50. The tract X_2X_3 recovers at such a rate that if only 50 impulses reach it in one second each impulse will fall in the phase of supernormal recovery, and will be large enough to pass the junction at X_3 and reach the muscle A. On the other hand, if the impulses occur at a frequency of 100 a second each will fall in the phase of subnormal recovery, and none of them will be large enough to

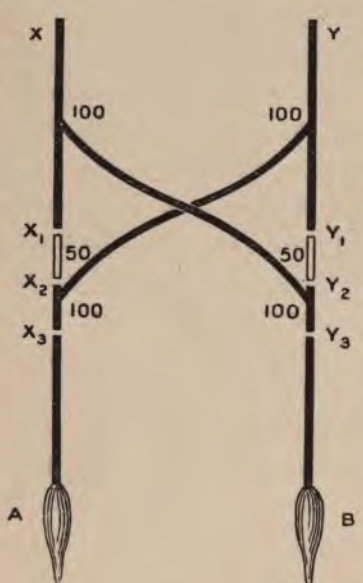

FIG. 22.

pass the junction at X_3. Thus the stimuli at X will give a contraction in A and the stimuli at Y will have no effect. Actually A is in a state of slight tonic contraction which we may suppose to be maintained by impulses arriving at X_2 from some other part of the central nervous system. The impulses from Y will reduce these also and so there will be a relaxation of the muscle when Y is stimulated. The same arrangement in the case of the muscle B will lead to inhibition following stimulation of X and contraction following stimulation of Y.

This hypothesis seems feasible enough though there are certain important objections to it which will be dealt with later. It is supported by various observations which show that the nature of the response in the reflex preparation depends on the strength and frequency of the stimuli and also on the degree of decrement just as it does in simple tissues. In the muscle-nerve preparation we have seen that the inhibitory effect is produced by the extinction of impulses which follow so closely that they are all of subnormal intensity; thus the failure to reach the muscle will depend on the frequency of the impulses, the rate of recovery of the tissue and the degree of decrement which each impulse must sustain on its journey to the muscle. An increase in the strength of the stimuli may also lead to inhibition because it will increase the frequency of the impulses set up. Now in the case of reflex inhibition there are several instances in which an increase in the strength or frequency of stimulation converts an excitatory stimulus into an inhibitory. Sherrington and Sowton[1] found that stimulation of the popliteal by weak rheonome currents caused a contraction in the extensors of the leg, whereas stimulation by weak currents from an induction coil gave inhibition. They suggest that the difference was due to the form of the stimulus employed, the rheonome current rising gradually to its maximum and the induced current rising much more steeply. However, we have no valid reasons for supposing that the form of an individual nervous impulse does depend on the form of the stimulus which sets it up, and it seems reasonable to assume

[1] Sherrington and Sowton, "Proc. Roy. Soc. B.," lxxxiii. p. 435, 1911.

that the stimuli differed not only in form but also in frequency. The rheonome currents were repeated at the rate of twenty a second, whereas the stimuli from an ordinary induction coil would recur at a much greater frequency, and this might easily account for the fact that the rheonome gave a reflex contraction and the induction coil an inhibition. A more definite result is given by the experiments of Tiedermann[1] on the effects of varying frequency of stimulation in the frog under the influence of strychnine. In this case the conversion of excitation into inhibition by an increase in the rate of stimulation is shown very clearly, and there is a further likeness to peripheral inhibition in that a series of rapidly repeated stimuli sometimes produces an initial twitch followed by inhibition just as it does in a fatigued muscle-nerve preparation.

Both Tiedermann and Veszi[2] have shown that inhibition may be produced by the simultaneous stimulation of two roots in the cord when the stimulation of either root alone will give a contraction. Here again the effect would seem to depend on the increased frequency of the impulses which would reach the final common path when both roots are stimulated at once.

The effect of increasing the strength of the stimuli was also investigated by Sherrington and Sowton.[3] They found that weak stimulation of the popliteal gave a contraction in the extensors, or else an initial contraction followed by inhibition. Strong stimuli invariably gave inhibition.

A reversal of the reflex effect is also produced by the action of certain drugs on the central nervous system. Bayliss[4] has shown that stimulation which normally leads to a vaso-constrictor reflex gives only vaso-dilatation after chloroform has been administered. Sherrington and Sowton[5] found the same reversal in a limb reflex. Now the most important action of chloroform in a peripheral nerve is to produce a decrement in conduction,

[1] Tiedermann, "Ztsch. f. allg. Physiol.," x. p. 183, 1910.
[2] Veszi, "Ztschr. f. allg. Physiol.," xi. p. 168, 1911.
[3] Sherrington and Sowton, loc. cit.
[4] Bayliss, "Proc. Roy. Soc. B.," lxxx. p. 365, 1908.
[5] Sherrington and Sowton, "Journ. of Physiol.," xlii. p. 383, 1911.

and therefore it is only to be expected that in the central nervous system it would increase the already existing decrements in the path of conduction and so lead to the extinction of impulses which were formerly just large enough to reach the motor neuron.

Evidence of this kind is not in any sense conclusive, but it lends some colour to the view that a process analogous to the apparent inhibition of Wedensky may be a normal event in the central nervous system. However, there are several difficulties to be faced. In the first place, reflex inhibition does not amount to a mere prevention of active contraction in the muscle, but to the abolition of a continued state of tone. The inhibition of active contraction is easily explained, but we are on more doubtful ground in dealing with the tonic contraction. We have assumed that it is maintained by a series of impulses which do not differ in kind from those we have studied in isolated nerve, but the phenomena of decerebrate rigidity give some grounds for believing that an entirely different mechanism is at work.[1] It is true that Buytendick[2] finds that the electric response of a muscle in decerebrate rigidity has the usual oscillating character, but there is reason to suppose that the energy exchanges of a muscle in this condition are less than they would be if the tone were due to the fusion of repeated small contractions.[3] The suggestion is that the tone of voluntary muscles in connection with the central nervous system, and in particular the state of decerebrate rigidity, is a steady condition analogous to that found in smooth muscle, in the lobster's claw, the adductor of pecten, etc., and presided over by a special set of nerve-fibres or by a special form of nervous impulse. On the other hand, it seems unlikely that the mechanism by which a tonic contraction is inhibited is radically different from that which cuts short an active reflex contraction. When the inhibitory nerve is stimulated it makes no difference whether the muscle is actively contracting in response to reflex excitation or is merely in the state of tone or of decerebrate

[1] See Bayliss, "Principles of General Physiology," pp. 540-6, 1915.
[2] Buytendick, "Ztschr. f. Biol.," lix. p. 36, 1912.
[3] Roaf, "Quart. Journ. Exper. Physiol.," v. p. 31, 1912.

rigidity; in either case it is thrown into complete relaxation, and it would at least make for economy if the process of inhibition were the same for the active contraction as for the tonic, depending in either case on the extinction of excitatory impulses which were formerly able to reach the muscle. Still there may be several distinct forms of inhibition in the central nervous system, one depending on the extinction of impulses and another on a general depression of function in the inhibited tissue, as in the action of the vagus on the heart. Evidently an analysis of tonic contraction is of very great importance, and until it has been carried out we cannot say that the mechanism of "apparent inhibition" gives a satisfactory explanation of all forms of central inhibition.

Even more important is the question of the balanced effects of inhibitory and excitatory stimuli. Sherrington[1] has shown in the case of the voluntary muscles and Bayliss[2] in that of the vaso-motor reflexes that if an excitatory and an inhibitory nerve are stimulated at the same time the effect produced is a simple algebraic summation of the two single effects and depends entirely on the relative strength of the two stimuli. Now according to the scheme in Fig. 22 it appears that a combined stimulation of the two nerves should always result in an inhibition. The frequency of the impulses in the central paths should be, if anything, greater when both nerves are stimulated than when the inhibitory nerve is acting by itself. Thus the impulses should be still further reduced in size and no excitation could result. Indeed the stimulation of several afferent nerves in connection with the final common path should always result in an inhibition whatever their effects might be when acting alone. Sometimes this proves to be the case; for instance, Veszi found that stimulation of the eighth or ninth dorsal root of the frog under strychnine caused a contraction in the gastrocnemius, whereas stimulation of both together gave inhibition. Tiedermann gives several examples of the same kind. However, Sherrington's records show clearly that a strong stimulation of the excitatory nerve may

[1] Sherrington, "Proc. Roy. Soc. B.," lxxx. p. 565, 1908.
[2] Bayliss, "Journ. of Physiol.," xiv. p. 303, 1893.

break through a simultaneous inhibition and cause a contraction instead of increasing the inhibition. It is evident that the scheme in Fig. 22 as it stands will not account for this effect.

We can, of course, fall back on the possibility that there are many fibres in the afferent nerves and that some of these would be unaffected by weak stimuli. We should have to suppose that the excitation was due to a series of conducting paths which were not thrown into action by the inhibitory stimulus because the fibres in the inhibitory nerve leading to these paths were relatively inexcitable. However, it is very doubtful if this explanation would account for all the facts, and in particular it does not explain the rhythmic contractions which sometimes result from stimulation of an excitatory and an inhibitory nerve at the same time. No doubt the difficulty could be overcome by introducing various subsidiary hypotheses, but there is little to be gained by elaborating a scheme in this way when its foundations are none too secure. We need to know more about the rate of recovery in sensory nerves and about the effects of alterations in the strength of the stimulus. We are not even certain that the all-or-none relation between the stimulus and the nervous impulse holds good for sensory nerves as it does for motor. Forbes[1] has shown recently that, in cases where a single stimulus is able to set up a reflex contraction, an increase in the stimulus leads to an increase in the reflex response, although the strength of the stimulus may be far greater than that required to set up a maximal electric response in the sensory nerve. He suggests the explanation that a strong stimulus may set up more than one impulse in the nerve. This would account for many of the reflex phenomena which follow an increase in the stimulus, but even so it is not easy to explain the balance between excitation and inhibition. Until this and similar points are settled we must be content to recognise the difficulty and await further evidence.

So far we have confined our attention to inhibition and summation, and we have attempted to show that they do not involve any properties which are peculiar to the central nervous system

[1] Forbes, "Amer. Journ. Physiol.," xxxix. p. 172, 1915.

and unknown to simple conducting tissues. It remains to discuss very briefly some other characteristics of central conduction which appear to be absent, or very poorly developed in peripheral tissues. In the first place, there is the well-known observation that conduction in the central nervous system proceeds in one direction only, from the afferent nerve to the efferent, and not vice-versa. This is certainly not peculiar to the central nervous system, for conduction in one direction only is found at the junction between nerve and muscle. Its mechanism is not clear and has not attracted much attention; the most likely explanation seems to be that it is due to differences in the rate of development of the impulse on either side of the junction, i.e. to Lapicque's heterochronism.[1] In this case it should be possible to reproduce it in a simple conducting tissue, and in fact Engelmann[2] has already done this in a sartorius by maintaining the two halves of the muscle at different temperatures or under the influence of different drugs.

Fatigue is another characteristic feature of reflex conduction as opposed to conduction in a simple tissue, but here again the central nervous system has no monopoly, for fatigue is shown by the nerve-ending and also by a simple tissue which is conducting imperfectly. As an example of this we may take Thörner's observation[3] that in a nerve treated with nitrogen conduction is extinguished sooner when impulses are passing down the nerve than when it is at rest. The same effect is sometimes found when the nerve has been treated with alcohol instead of nitrogen. Evidently the continued passage of impulses increases the difficulty in conduction in a region of decrement, just as it does in the central nervous system. There is a further possibility that some of the phenomena of central fatigue might be due to a lengthening of the refractory period at some point in the conducting path; however, such a lengthening has not yet been clearly demonstrated in simple tissues.

[1] Lapicque, "C. R. Soc. de Biol.," lxxii. p. 283, 1912.
[2] Engelmann, "Arch. f. d. ges. Physiol.," lxii. p. 400, 1896.
[3] Thörner, "Ztschr. f. allg. Physiol.," viii. p. 530, 1908; x. p. 351, 1910.

One other property of the central nervous system deserves mention. This is its capacity to respond to a single afferent impulse with a series of discharges. The most striking demonstration of this is given by reflex preparations under the influence of strychnine, where a single stimulus to an afferent nerve produces a train of electric responses in the efferent.[1] However, the effect is undoubtedly met with under normal conditions as well, for there are many reflexes in which the response outlasts the stimulus by several seconds. The same repeated discharge to a single stimulus has been found by Gotch and Burch in the electric organ of Malapterurus,[2] and on these grounds the effect is sometimes regarded as peculiar to the nerve-cell as distinguished from the nerve-fibre. Certainly it is not present in simple conducting tissues under ordinary conditions, but we have at least an indication of it in the phenomena of recovery in nerve. We have seen that in the period of supernormal recovery following the refractory phase the excitability is raised above its normal value. As a rule the increase of excitability is not very great, but it is quite conceivable that in special tissues it might be very much greater, so great indeed that a second impulse would be set up by an extremely weak stimulus or even by none at all. Thus a single stimulus would suffice to set up a train of disturbances which would continue as long as the excitability rose to infinity during each supernormal phase. From another point of view the multiple responses of the central nervous system may be likened to the rhythmic contractions which appear in striated muscle in the absence of certain ions. Here the discharge continues indefinitely without any external stimulus, but it is easy to imagine an intermediate stage in which the automatic action is not so fully developed, needing a stimulus to initiate it and dying down after a few responses.

All this may seem a laboured attempt to magnify the likeness between peripheral and central conduction beyond all reason. The likeness may be there, but why insist on it at such

[1] Veszi, "Ztschr. f. allg. Physiol.," xv. p. 245, 1913.
[2] Gotch and Burch, "Phil. Trans.," clxxxvii. p. 347, 1896.

length? The answer is that it is very much easier to investigate a simple case than a complex. If we have reasonable ground for supposing that the process of conduction depends on much the same mechanism in the central nervous system as in the peripheral nerve, it will be worth while to analyse the mechanism of peripheral conduction as fully as possible in the hope that we may learn more of the workings of the central nervous system. If the central nervous system involves processes which are entirely unknown in peripheral nerve, then the analysis of peripheral conduction loses a great deal of its interest and the problem of central conduction becomes infinitely more formidable. Indeed the complex structure of the central nervous system would make it almost impossible to attempt more than the most superficial analysis, if all our information is to be drawn from the central nervous system alone. But if we can assume that the same laws govern the conduction of an impulse in the central nervous system and in a peripheral nerve, the problem becomes very much simpler. In a muscle-nerve preparation it is possible to control every important factor to a degree which would be quite out of the question in the central nervous system, and our analysis of peripheral conduction, though far from complete, is still advanced enough to allow us to predict what will happen in different circumstances with a fair degree of accuracy. On the basis of this analysis we have pictured the central nervous system as a network of conductors having different refractory periods, communicating through regions of decrement, easily fatigued and capable of setting up a train of impulses in answer to a single stimulus. Several difficulties have been mentioned already, and it would not be hard to find others. Whether they can be solved without introducing any new factors in central conduction is a question which must be left for future experiment to decide. In any case it will be worth while to continue the investigation on these lines until we find clear evidence of a mechanism of conduction in the central nervous system which differs fundamentally from that found in simple tissues such as muscle and nerve.

PRINTED IN GREAT BRITAIN BY THE UNIVERSITY PRESS, ABERDEEN